09/885783

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

OIPE JC77
08 2002
PATENT & TRADEMARK OFFICE

EXAMINER

ART UNIT	PAPER NUMBER

DATE MAILED:

DEC - 2 1999

PRACTICE SYSTEMS

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

RECEIVED
JUL 1 5 2002
TECH CENTER 1600/2900

Docketed By Practice Systems
Action Code: Restriction Requirement
Base Date: 11/26/99
Due Date: 12/26/99
Deadline: 5/26/2000
Initials: jgencheson
Record: n/a

Docketed By Billing Secretary
Due Date: 12/26/94
Deadline: 5/26/2000
Initials: JGW

Office Action Summary	Application No.	Applicant(s)	
	09/177,164	PONIKAU, JENS	
	Examiner	Art Unit	
	Victor Oke	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133)

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-69 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims 1-69 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☐ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims1 – 59, drawn to method, article of manufacture and composition, and the method of making the same for treating non invasive fungus-induced rhinosinusitis, classified in class 514, subclass, 252, and class 514, subclass, 31.

II. Claim 60 drawn to method of culturing fungus classified in class 435, subclass 254.1+

III. Claim 61, drawn to method of obtaining a fungal antigen classified in class 424 subclass 275.1.

IV. Claim 62, drawn to method of producing fungus-specific antibody classified in class 424 subclass 171.1.

V Claim 63-65, drawn to nasal mucus collecting apparatus, classified in class 604, subclass 19+

VI. Claim 66-69, drawn to pharmaceutical composition, classified in class 514, subclass 252, and class 514, subclass 31.

Inventions VI and I are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions I and VI would be expected to have

different modes of operation, different function and different effect. For example, one of the compositions of group VI contains an anti-fungal agent as well as mucolytic agent, and would be expected to have mucolytic as well as anti-fungal effect whereas the compositions of group I would be expected to primarily have an anti-fungal effect. Each of groups II, III, IV, and V is directed to a separate and distinct inventions, group II is directed to method of culturing fungus; group III is directed to method of obtaining a fungal antigen; group IV is directed to method of producing fungus-specific antibody; and group V is directed to nasal mucus collection apparatus.

The products of groups II, III, IV, and V respectively, would be expected to have distinct morphological, functional, chemical and physical properties as evidenced by divergent classification, process of making and process of using. These products are capable of separate manufacture, use, or sale as claimed, and are patentable over each other (though they may each be unpatentable because of the prior art) subjects.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

If applicant elects group I further election of species is required.

This application contains claims directed to the following patentably distinct species of the claimed invention: directed to solid, liquid or aerosol form.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-8,12-19, 27-54 is generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

The above restriction/election requirement is complex and as such a telephone call to the attorney to request an oral election was not made. (see MPEP 812.01)

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Victor Oke whose telephone number is (703) 308-8869. The examiner can normally be reached on Monday to Friday from 8:00 am to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald E. Adams (Ph.D.), can be reached on (703) 308-0570. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Victor Oke 11/19/99

MINNA MOEZIE
PRIMARY EXAMINER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Jens Ponikau
Serial No. : 09/177,164
Filed : October 22, 1998
Title : METHODS AND MATERIALS FOR TREATING AND PREVENTING INFLAMMATION OF MUCOSAL TISSUE

Art Unit : 1617
Examiner : Victor Oke

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO RESTRICTION REQUIREMENT

Responsive to the action mailed November 26, 1999, Applicant elects the invention of Group I (claims 1-59). The election of Group I is made without traverse. In addition, Applicant elects the species directed to a liquid form. Claims 1-9 and 12-59 read on this species. The election of the species directed to a liquid form is made without traverse.

Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: December 7, 1999

J. Patrick Finn III, Ph.D.
Reg. No. 44,109

JXF/jxf

Fish & Richardson P.C., P.A.
60 South Sixth Street, Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

60003184.doc

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

December 7, 1999
Date of Deposit

Signature

Judith A. Wasillus
Typed or Printed Name of Person Signing Certificate

MSE
JT

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

RECEIVED
MAR - 6 2000
PRACTICE SYSTEMS

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Docketed By Practice Systems
Action Code: Response to Office Action
Base Date: 2/29/00
Due Date: 5/29/00
Deadline: 8/29/00
Initials: JBeuchler
Record: n/a

Docketed By Billing Secretary
Due Date: ✓
Deadline: ✓
Initials: BB SVB

PTO-90C (Rev. 2/95)

2 - Mail Copy

Office Action Summary	Application No.	Applicant(s)	
	09/177,164	PONIKAU, JENS	
	Examiner	Art Unit	
	Victor Oke	1617	

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Period for Reply

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Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *10,11 and 60-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 12-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

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14) ☐ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,9,12,13*
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other:

(4)

DETAILED ACTION

1. Applicant's election without traverse of invention of group I, claims 1-59, and the liquid form specie in Paper No. 11 submitted December 10, 1999 is acknowledged.

2. Claims 10-11 and 60-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Claim Objections

Claims 40-41, 56 and 57 are objected to because of the following informalities: the expressions "the said formulation comprises" and "the said method comprise" are unclear as to whether an additional method step or formulation ingredient is intended. The expression, "further comprises" is suggested.

3. Claim 27 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. A plurality of antifungal agents does not constitute a further limitation to the single antifungal agent recited in

claim 1. The employment of "further comprising" language is suggested if additional antifungal agents are intended to be employed in the method of claim 1.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the employment of specified "therapeutic" compounds, (see, e.g. page 45, lines18-25, including amphotericin B and itraconazole as in the examples at pages 51-72 in the specification), and antifungal agents at page 38, lines 10-19 in the specification, does not reasonably provide enablement for the employment of any compounds deemed "therapeutic" in some respect. Further, the specification does not provide enablement for a second formulation containing any ingredients as in claim 41. The second formulation as claimed can employ any unrelated compounds and can be administered by any route. See, page 49, lines 18-25. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/use the invention commensurate in scope with these claims. The claims encompass the employment of a wide range of unrelated compounds, which can be termed "therapeutic compounds" or useful in "a second formulation".

6. One of ordinary skill would not reasonably expect all such compounds to have the same or sufficiently similar properties to be similarly useful herein.

7. Applicant's disclosure provides insufficient direction, guidance and/or working examples showing how to make and/or use any compounds deemed "therapeutic" or any second formulation in the claimed methods of treatment and compositions. Note that all examples in the specification appear to be directed to amphotericin B and itraconazole as antifungal therapeutic agents.

8. One of ordinary skill would be required to perform undue experimentation to determine, which compounds would share sufficient specific activity or properties with those compounds particularly disclosed herein to be similarly useful in the claimed formulation or method of antifungal treatment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 3, 8, 45, 47, 48 and 50 are rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 45, 48, and 50 recite the term "a mammal at risk" for developing non-invasive fungus-induced rhinosinusitis. The claims are indefinite as to mammals encompassed thereby.

10. Claim 3 recites the term "nonatopic". The term is confusing as to how the mammalian host recited in the base claim is further limited.

11. Claim 8 recites the term "partial liquid". It is unclear what forms are encompassed by the term "partial liquid".

12. Claim 47 recites the term "diagnosing". The claim is indefinite as to what is being diagnosed. The claim sentence appears to be incomplete.

13. The claims of this application have been examined insofar as they read on the elected invention and species.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-9, 13-16, 17-18, 20-21, 30, 40, and 46-47 are rejected under 35 U.S.C. 102(a) as being anticipated by Bent III et al. Laryngoscope 106: November 1996.

16. Bent teaches the use of topical antifungal irrigation in the treatment of allergic fungal sinusitis, e.g., employing amphortericin B and ketoconazole. See e.g., page 1331, the second column, second paragraph, the discussion on page 1333, second column and the conclusion on page 1334.The reference teaches a therapeutic antifungal solution of 1 mg/mL ketoconazole, see page 1333, column 1, last paragraph. Bent further teaches that proper identification of the disease is essential and the method thereof. See page 1333, column 2, second paragraph.

17. Claims 1-9, 13, 16, 20, 22-24, 30-32, 34-36, 40-42 and 46-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Bassiouny et al. J. of Laryngol Otol., March 1982; 96(3).

18. Bassiouny teaches the treatment of fungal nasal sinusitis using paranasal irrigation and daily instillation of 20 ml of clotrimazole solution. See the abstract, cases and treatment on pages 223-225. The reference teaches a bi-weekly antral washout followed by instillation of 20 ml clotrimazole solution for four consecutive weeks. See treatment on pages 224 and 225. The reference teaches that identification and proper diagnosis of the patient is important and teaches the method thereof. See page 226, fourth paragraph bridging page 227.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 12, 19, 22-29, 31-39, 41-45 and 48-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over John P. Bent III et al, Laryngoscope 106: November 1996

Bent teaches the use of topical antifungal irrigation in the treatment of allergic fungal sinusitis, e.g., employing amphotericin B and ketoconazole. See e.g., page 1331 the

second column, second paragraph, the discussion on page 1333 and the conclusion on page 1334. The reference teaches a therapeutic antifungal solution of 1 mg/mL of Ketoconazole, see page 1333, column 1, last paragraph. The reference further teaches that proper identification of the disease is essential and the method thereof. See page 1333, column 2, second paragraph.

4. The primary reference does not teach the use of macrolide antifungal, the use of the particular antifungal itraconazole, the effective amounts herein; frequency or duration of treatment claimed herein, the use of the second formulation herein, preventive treatment or the article of manufacture, or formulation and its method of manufacture.

5. One of ordinary skill in the art would have found it obvious to modify the primary reference by employing the effective amounts, and the frequency or duration of treatment herein, using the second formulation herein, employing the claimed method in preventive treatment, and employing such antifungal compounds in the article of manufacture or composition herein.

6. A person of ordinary skill in the art would have been motivated to make these modifications because; any known antifungal agent would be expected to be similarly useful. Optimization of the amount to be administered or dosage of an active agent is considered within the skill of the artisan. Further the employment of a second

formulation containing topical steroid is motivated since these agents are known to be useful to treat allergic fungus sinusitis. See page 1331, column 2 in Bent.

The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungus sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would be expected.

The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents is known in the treatment of allergic fungus sinusitis. See e.g., page 1333, column 1 in Bent. Finally, the method of making a composition by mixing or combining ingredients is considered prima facie obvious.

7. Claims 12,14-15,17-19,21, 25-29, 33, 37-39, 43-45, and 48-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bassiouny et al. J. of Laryngol Otol., March 1982; 96(3) and Morpeth et al. Annals of Allergy, Asthma, and Immunology, Volume 76: 128-40, 1996.

Bassiouny teaches the treatment of fungal nasal sinusitis using paranasal irrigation and daily instillation of 20 ml of clotrimazole solution. See the abstract, cases and treatment on pages 223-225. The reference teaches a bi-weekly antral washout followed by instillation of 20 ml of clotrimazole solution for four consecutive weeks. See treatment on pages 224 and 225. The reference teaches that identification and proper diagnosis

of the patient is important and teaches the method thereof. See page 226, fourth paragraph bridging page 227.

8. Morpeth teaches the use of saline irrigation followed by topical intranasal administration of corticosteroids and antifungal agents. See page 134, column 3, second paragraph.

9. The references do not teach the employment of macrolide, sterol inhibitor and cell wall interpolator antifungals, effective amounts, frequency or duration of treatment claimed herein, preventive treatment or the article of manufacture or formulation and its method of manufacture.

A person of ordinary skill in the art would have been motivated to make these modifications because; any known antifungal agents would be expected to be similarly useful. The employment of a composition which is known to be useful in the treatment of a disorder such as allergic fungus sinusitis, in the prevention of the same disorder is considered clearly obvious as therapeutic effects would be expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungal sinusitis is motivated by the prior art since topical irrigation with antifungal agents is known in the treatment of allergic fungus sinusitis. See e.g., page 1333, column 1 in Bent. Finally, the method of making a composition by mixing or combining the ingredients is considered prima facie obvious.

References herein cited have been provided by applicant in the IDSs, of paper numbers 7,9 and 12 submitted Mar.16, Aug. 24 and Dec. 16, 1999 respectively.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Victor Oke whose telephone number is (703) 308-8869. The examiner can normally be reached on Monday to Friday from 8:00 am to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald E. Adams Ph.D., can be reached on (703) 308-0570. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Victor Oke
1/21/00

MINNA MOEZIE
PRIMARY EXAMINER

Applicant Copy

Sheet 1 of 1

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 07039-104001	Application No. 09/177,164
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Jens Ponikau	
(37 CFR §1.98(b))		Filing Date October 22, 1998	Group Art Unit 1617

U.S. Patent Documents

Examiner Initial	Desig. ID	Patent Number	Issue Date	Patentee	Class	Subclass	Filing Date If Appropriate
V.O.	AA	5,897,872	4/27/99	Picciano			11/12/97
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						

OIPE JC33 FEB - 7 2000 PATENT & TRADEMARK OFFICE

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
	AL							
	AM							
	AN							
	AO							
	AP							

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	AQ	
	AR	
	AS	
	AT	

Examiner Signature	Date Considered
V. Olke	2/24/00

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form (PTO-1449)

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 07039-104001	Application No. 09/177,164
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))		Applicant Jens Ponikau	
		Filing Date October 22, 1998	Group Art Unit 1617

U.S. Patent Documents

Examiner Initial	Desig. ID	Patent Number	Issue Date	Patentee	Class	Subclass	Filing Date If Appropriate
V.O.	AA	4,883,785	11/28/89	Chow et al.			
	AB						

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
V.O.	AC	WO95/08993	06.04.95	PCT				
V.O.	AD	WO97/03651	06.02.97	PCT				
	AE							

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	AQ	Baumjohann et al., TW Gynakologie, "Rezidivierende Vaginal-und Darmmykosen, Vol. 4, pgs. 400-402, 1999
	AR	Cross, Chest, "Amphotericin B Aerosol for Transientyl Immunocompromised Hosts", Vol. 108, pgs. 599-601, 1995
	AS	V. Nolting et al., Fortschritte der Medizin, "Candida und der Intestinaltrakt", Vol. 115, pgs. 22-28, Feb. 1998
	AT	Purcell et al., Thorax, "Use of nebulised liposomal amphotericin B in the treatment of *Aspergillus fumigatus* empyema", Vol. 50, pgs. 1321-1323, 1995
	AU	S. Tiwari et al., Mycoses, "Chronic bilateral suppurative otitis media caused by *Aspergillus terreus*," Vol. 38, pgs. 297-300, 1995
V.O.	AV	Van Cutsem, Mycoses, "Oral, Topical and Parenteral Antifungal Treatment with Itraconazole in Normal and in Immunocompromised Animals, Vol. 32 (Suppl. 1), pgs. 14-34, 1989

Examiner Signature	Date Considered
V.O.	2-24-00

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 07039/104001	Serial No. 09/177,164
INFORMATION DISCLOSURE STATEMENT BY APPLICANT		Applicant: Jens Ponikau	
(37 CFR 1.98(b))		Filing Date: October 22, 1998	Group: 1615

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No

OTHER DOCUMENTS - Including Author, Title, Date, Pertinent Pages, Etc.

V.O.	AA	Bent JP and Kuhn FA, "Antifungal Activity Against Allergic Fungal Sinusitis Organisms," *Laryngoscope* 106:1331-1334 (1996)
V.O.	AB	Bassiouny A *et al.* "Non-invasive antromycosis (Diagnosis and treatment)," *J. Laryngol. Otol.* 96:215-228 (1982)

Examiner	Date Considered
	1/18/00

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U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date
V.O.	AA	5,707,975	1/13/98	Francois et al.	514	58	9/22/94
V.O.	AB	5,658,881	8/19/97	Gelland et al.	514	11	10/14/94
V.O.	AC	5,654,293	8/5/97	Francois et al.	514	171	1/12/94
	AD	5,441,977	8/15/95	Russo et al.	514	411	3/1/94
	AE	5,248,504	9/28/93	Friedman	424	434	3/2/92
	AF	5,080,899	1/14/92	Sturm et al.	424	122	2/22/91
	AG	5,075,309	12/24/91	Heeres et al.	514	252	5/1/90
	AH	4,916,134	4/10/90	Heeres et al.	514	252	4/7/89
	AI	4,432,991	2/21/84	Dusza et al.	424	273 P	11/1/82
	AJ	4,402,957	9/6/83	Heeres et al.	424	250	5/7/81
	AK	4,209,447	6/24/80	Heeres	260	340.9 R	12/1/78
V.O.	AL	3,929,992	12/30/75	Sehgal et al.	424	122	4/12/74

FOREIGN PATENT DOCUMENTS

	Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No

OTHER DOCUMENTS - Including Author, Title, Date, Pertinent Pages, Etc.

V.O.	AM	Cody *et al.*, "Allergic Fungal Sinusitis: The Mayo Clinic Experience," *Laryngoscope* 104:1074-1079 (1994)
V.O.	AN	Kupferberg SB *et al.*, Prognosis for Allergic Fungal Sinusitis," *Otolaryngol. Head Neck Surg* 117:35-41 (1997)
V.O.	AO	Quraishi *et al.*, "Endoscopic Treatment of Allergic Fungal Sinusitis," *Otolaryngol. Head Neck Surg.* 117:29-34 (1997)

Examiner		Date Considered	1/18/00

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V.O.	BA	Roth M, "Should Oral Steroids Be the Primary Treatment for Allergic Fungal Sinusitis?," *Ear, Nose & Throat J.* 73:928-930 (1994)
	BB	Bartynski *et al.*, Allergic Fungal Sinusitis Secondary to Dermatiaceous fungi-*Curvularia lunata* and *Alternaria*, *Otolaryngol. Head Neck Surg.* 103:32-39 (1990)
	BC	Sait *et al.*, "Oral Amphotericin B in the Treatment of Ulcerative Intestinal Diseases," *Digestive Diseases* 15:993-1002 (1970)
	BD	Pasha *et al.*, "Basidiobolomycosis: An Unusual Fungal Infection Mimicking Inflammatory Bowel Disease," *Gastroenterology* 112:250-254 (1997)
	BE	Dhindsa *et al.*, "Chronic Suppurative Otitis Media Caused by Paecilomyces variotii," *Journal of Medical & Veterinary Mycology* 33:59-61 (1995)
	BF	Tiwari *et al.*, "Chronic Bilateral Suppurative Otitis Media Caused by Aspergillus terreus," *Mycoses* 38:297-300 (1995)
	BG	Cohen, S.R., "Otitic Candidiasis in Children: An Evaluation of the Problem and Effectiveness of Ketoconazole in10 Patients," *Ann. Otol. Rhinol. Laryngol.* 99:427-431 (1990)
	BH	Falser N., "Fungal Infection of the Ear," *Dermatologica* 169(1):135-140 (1984)
	BI	Dunand *et al.*, "Parasitic Sinusitis and Otitis in Patients Infected with Human Immunodeficiency Virus: Report of Five Cases and Review," *Clinical Infectious Diseases* 25:267-272 (1997) (best copy available)
	BJ	Adam *et al.*, "Phaeohyphomycosis Caused by Fungal Genera *Bipolaris and Exserohilum*," *Medicine* 65(4):203-217 (1986)
	BK	Bent JP and Kuhn FA, "Antifungal Activity Against Allergic Fungal Sinusitis Organisms," *Laryngoscope* 106:1331-1334 (1996)
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	BM	Cayton *et al.*, "Double-Blind Trial Comparing Two Dosage Schedules of Beclomethasone Dipropionate Aerosol in the Treatment of Chronic Bronchial Asthma," *The Lancet* pp. 303-307 (1974)
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	BO	Corey *et al.*, "Allergic Fungal Sinusitis: Allergic, Infectious, or Both?", *Otolaryngol. Head Neck Surg.* 113:110-119 (1995)
	BP	Dubois *et al.*, "The Physiologic Effects of Inhaled Amphotericin B," *Chest* 108:750-753 (1995)
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Examiner	**Date Considered**
	1/18/00

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(37 CFR 1.98(b))		Filing Date: October 22, 1998	Group: 1615

OTHER DOCUMENTS - Including Author, Title, Date, Pertinent Pages, Etc.

	CA	Goldstein MF, "Allergic Fungal Sinusitis: An Underdiagnosed Problem," *Hospital Practice* pp. 73-74, 79-81, 83-84, 87-88, 91-92 (1992)
	CB	LeBeau *et al.*, "Itraconazole in the Treatment of Aspergillosis: A Study of 16 Cases," *Mycoses* 37:171-179 (1994)
	CC	Macmillan *et al.*, "Allergic Fungal Sinusitis Due to *Curvularia lunata*," *Hum. Pathol.* 18:960-964 (1987)
	CD	Mathews *et al.*, "Computed Tomographic Assessment of Noninvasive Intranasal Infusions in Dogs With Fungal Rhinitis," *Veterinary Surgery* 25:309-319 (1996)
	CE	McKendrick *et al.*, "Pulmonary Moniliasis Treated With Nystatin Aerosol," *The Lancet* pp. 621-622 (1958)
	CF	Meyer *et al.*, "Fungal Sinusitis in Patients With AIDS" Report of 4 Cases and Review of the Literature," *Medicine* 73(2):69-78 (1994)
	CG	Morgan *et al.*, "Fungal Sinusitis in Healthy and Immunocompromised Individuals," *Am. J. Clin. Pathol.* 82(5):597-601 (1984)
	CH	Morpeth *et al.*, "Fungal Sinusitis: An Update," *Annals of Allergy, Asthma & Immunology* 76:128-136, 139-140 (1996)
	CI	Ogawa K., "5. Treatment of Chronic Pulmonary Aspergillosis," *Japanese Society for Tuberculosis*, Kekkaku 72(2):59-64 (1997) (English translation attached)
	CJ	Philip G and Keen CE, "Allergic Fungal Sinusitis," *Brief Reports*, 14(2):222-224 (1988)
	CK	McKendrick and Medlock, "Pulmonary Moniliasis Treated With Nystatin Aerosol," *The Lancet* pp. 1229-1230 (1958)
	CL	Robb PJ, "Aspergillosis of the Paranasal Sinuses: A Case Report and Historical Perspective," *J. Laryngology and Otology* 100:1071-1077 (1986)
	CM	Robson *et al.*, "Allergic Fungal Sinusitis Presenting as a Paranasal Sinus Tumour," *Aust. NZ J. Med.* 19:351-353 (1989)
	CN	Rolston *et al.*, "Infections Caused by *Drechslera* Species: Case Report and Review of the Literature," *Reviews of Infectious Diseases* 7(4):525-529 (1985)
	CO	Shale *et al.*, "Trial of Ketoconazole in Non-invasive Pulmonary Aspergillosis," *Thorax* 42:26-31 (1987)
	CP	Slavin *et al.*, "Allergic Bronchopulmonary Aspergillosis: Characterization of Antibodies and Results of Treatment," *J. Allerg.* 46(3):150-155 (1970)
	CQ	Stark JE, "Allergic Pulmonary Aspergillosis Successfully Treated with Inhalations of Nystatin," *Diseases of the Chest* 51(1):96-99 (1967)

Examiner	**Date Considered** 1/18/20

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Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 07039/104001	Serial No. 09/177,164
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		Filing Date: October 22, 1998	Group: 1615

OTHER DOCUMENTS - Including Author, Title, Date, Pertinent Pages, Etc.

V.O.	DA	Travis *et al.*, "Unusual Aspects of Allergic Bronchopulmonary Fungal Disease: Report of Two Cases Due to *Curvularia* Organisms Associated With Allergic Fungal Sinusitis," *Human Pathology* 22(12):1240-1248 (1991)
	DB	Tsushima *et al.*, "Successful Treatment of Fungus Ball in a Patient with Allergic Bronchopulmonary Aspergillosis: Continuous Percutaneous Instillation of Antifungal Agents into the Cavity," *Internal Medicine* 35(9): 736-741 (1996)
	DC	Urakami *et al.*, "Clinical Features of Eight Cases of Opporunistic Fungal Pneumonias," Fourth Department of Internal Medicine, Kinki University School of Medicine, Osakasayama, Japan (English only)
	DD	Wengrower *et al.*, "Bronchopulmonary Candidiasis Exacerbating Asthma," *Respiration* 47:209-213 (1985)
	DE	Zieske *et al.*, "Dematiaceous Fungal Sinusitis," *Otolaryngol. Head Neck Surgery* 105(4): 567-577 (1991)
	DF	Swift *et al.*, "Skull Base Osteitis Following Fungal Sinusitis," *J. Laryngology and Otology* 112:92-97 (1998) (best copy available)
	DG	Bent JP and Kuhn FA, "Diagnosis of Allergic Fungal Sinusitis," *Otolaryngol. Head Neck Surg.* 111:580-588 (1994)
	DH	deShazo RD and Swain RE, "Diagnostic Criteria for Allergic Fungal Sinusitis," *J. Allergy Clin. Immunol.* 96:24-35 (1995)
	DI	Kilburn KH, "The Innocuousness and Possible Therapeutic Use of Aerosol Amphotericin-B," U.S. Army Medical Research & Nutrition Laboratory, Fitzsimons Army Hospital, Denver, Colorado, pp. 441-442 (1959)
	DJ	Kintzel PE *et al.*, "Otic Adminstration of Amphotericin B 0.25% in Sterile Water," *Ann. Pharmacother.* 28(3):333-335 (1994)
	DK	Denning *et al.*, "Adjunctive Therapy of Allergic Bronchopulmonary Aspergillosis with Itraconazole," *Chest* 100:813-819 (1991)
	DL	Nicolau *et al.*, "Rifampin-Fluconazole Interaction in Critically Ill Patients," *The Annals of Pharmacotherapy* 29:994-996 (1995)
	DM	Purcell IF and Corris PA, "Use of Nebulised Liposomal Amphotericin B in the Treatment of *Aspergillus fumigatus* Empyema," *Thorax* 50:1321-1323 (1995)
V.O.	DN	Farquhar *et al.*, "Ketoconazole and Fungal Sinusitis," *Scott Med. J.* 29:192-193 (1984)

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	1/18/00

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Jens Ponikau
Serial No. : 09/177,164
Filed : October 22, 1998
Title : METHODS AND MATERIALS FOR TREATING AND PREVENTING INFLAMMATION OF MUCOSAL TISSUE

Art Unit : 1617
Examiner : Victor Oke

Assistant Commissioner for Patents
Washington, D.C. 20231

AMENDMENT

In response to the action mailed February 29, 2000, please amend the application as follows:

In the Claims:

Please cancel claims 41, 47, and 60-69 without prejudice.

Please amend claims 8, 40, 42, 56, and 57 as follows.

8. (Amended Once) The method of claim 1, wherein said formulation is in a form selected from the group consisting of a powder, crystalline substance, gel, paste, ointment, salve, cream, solution, suspension, [partial liquid,] spray, nebulae, mist, atomized vapor, aerosol, and tincture.

40. (Amended Once) The method of claim 1, wherein said formulation further comprises a compound selected from the group consisting of pharmaceutically acceptable aqueous vehicles, pharmaceutically acceptable solid vehicles, mucolytic agents, antibacterial agents, anti-inflammatory agents, immunosuppressants, dilators, vaso-constrictors, and steroids[, and therapeutic compounds].

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

May 23, 2000
Date of Deposit

Signature

Jill A. Huso
Typed or Printed Name of Person Signing Certificate

42. (Amended Once) The method of claim 1 [41], wherein said method further comprises administering to said mammal a second formulation, said second formulation comprising [comprises] a compound selected from the group consisting of antifungal agents, pharmaceutically acceptable aqueous vehicles, pharmaceutically acceptable solid vehicles, mucolytic agents, antibacterial agents, anti-inflammatory agents, immunosuppressants, dilators, vaso-constrictors, and steroids[, and therapeutic compounds].

56. (Amended Once) The antifungal formulation of claim 55, wherein said formulation further comprises polyethylene glycol.

57. (Amended Once) The antifungal formulation of claim 55, wherein said formulation further comprises a flavoring.

Please add claims 70-72 as follows:

--70. The method of claim 1, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

71. The method of claim 70, wherein said mammal had a nasal surgery before said mucoadministration.

72. The method of claim 70, wherein said mammal was nasal surgery-free before said mucoadministration.--

REMARKS

The Examiner rejected claims 1-9 and 12-59 and withdrew claims 10, 11, and 60-69 from consideration. Claims 41, 47, and 60-69 have been cancelled, and claims 8, 40, 42, 56, and 57 have been amended. In addition, new claims 70-72 have been added herein. Thus, claims 1-40, 42-46, 48-59, and 70-72 are pending. No new matter is added by these

amendments. In light of these amendments and the following remarks, Applicant respectfully requests reconsideration and allowance of claims 1-9, 12-40, 42-46, 48-59, and 70-72.

Claim Objections

The Examiner objected to claims 40, 41, 56, and 57, suggesting the use of "further comprises." Claim 41 has been cancelled herein, and claims 40, 56, and 57 have been amended herein according to the Examiner's suggestions.

In addition, the Examiner objected to claim 27 under 37 CFR §1.75(c) as being in improper dependent form for failing to further limit the subject matter of a previous claim, again suggesting the use of "further comprising." Applicant respectfully disagrees. Claim 1 recites a formulation comprising an antifungal agent. Thus, the formulation can have a single antifungal agent or multiple antifungal agents. Claim 27 indicates that the formulation of claim 1 comprises a plurality of antifungal agents. Thus, the formulation recited in claim 27 limits the formulation of claim 1 to those formulations containing multiple antifungal agents. In light of the further limitation provided by claim 27, Applicant respectfully requests withdrawal of the objection to claim 27.

Rejections under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 40-42 under 35 U.S.C. §112, first paragraph, indicating that the specification does not provide enablement for (1) the use "of any compound deemed 'therapeutic' in some respect," and (2) "a second formulation containing any ingredients . . . ."

Applicant respectfully submits that the present specification fully enables claims 40-42. To expedite prosecution, however, claim 41 has been cancelled, and claims 40 and 42 have been amended to delete the term "therapeutic compounds." In light of these amendments, Applicant respectfully requests withdrawal of the rejection of claims 40 and 42 under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner rejected claim 3 under 35 U.S.C. §112, second paragraph, stating that the term "nonatopic" is confusing as to how the mammalian host recited in the base claim is further limited. Applicant respectfully submits that the mammal recited in claim 1 can be atopic or nonatopic. The mammal recited in claim 3 is limited to a nonatopic mammal. In light of this explanation, Applicant respectfully requests withdrawal of the rejection of claim 3 under 35 U.S.C. §112, second paragraph.

The Examiner also rejected claim 8 under 35 U.S.C. §112, second paragraph, stating that "it is unclear what forms are encompassed by the term 'partial liquid.'" Applicant respectfully submits that a skilled artisan would understand the meaning of a partial liquid. To expedite prosecution, however, claim 8 has been amended herein to delete the term "partial liquid." In light of this amendment, Applicant respectfully requests withdrawal of the rejection of claim 8 under 35 U.S.C. §112, second paragraph.

In addition, the Examiner rejected claims 45, 48, and 50 under 35 U.S.C. §112, second paragraph, stating that the claims are indefinite as to what mammals are encompassed by the term "a mammal at risk for developing non-invasive fungus-induced rhinosinusitis." Applicant respectfully submits that specification discloses mammals that are at risk for developing non-invasive fungus-induced rhinosinusitis. See, e.g., page 29, line 27 through page 30, line 3 of Applicant's specification. For example, elderly individuals as well as individuals having cystic fibrosis, asthma, and a family history of nasal problems or allergies can be at risk for developing non-invasive fungus-induced rhinosinusitis. In light of Applicant's disclosure, Applicant respectfully requests withdrawal of the rejection of claims 45, 48, and 50 under 35 U.S.C. §112, second paragraph.

Further, the Examiner rejected claim 47 under 35 U.S.C. §112, second paragraph, stating that the claim is indefinite as to what is being diagnosed. Claim 47 has been deleted herein. Thus, this rejection is moot.

Rejections under 35 U.S.C. §102(a)

The Examiner rejected claims 1-9, 13-18, 20, 21, 30, 40, 46, and 47 under 35 U.S.C. §102(a) as being anticipated by Bent *et al.* (Laryngoscope 106:1331-1334 (1996)). Specifically, the Examiner stated that the Bent *et al.* reference teaches (1) the use of topical antifungal irrigation in the treatment of allergic fungal sinusitis, and (2) a therapeutic antifungal solution of 1 mg/mL ketoconazole. In addition, the Examiner stated that the Bent *et al.* reference "teaches that proper identification of the disease is essential and the method thereof."

Applicant respectfully disagrees. At no point does the Bent *et al.* reference disclose the successful treatment of allergic fungal sinusitis. In fact, the authors of the Bent *et al.* reference specifically state that they "attempted intraoperative and postoperative topical irrigations with fluconazole without success." Moreover, the present claims require the direct mucoadministration of a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate non-invasive fungus-induced rhinosinusitis. At no point does the Bent *et al.* reference disclose these features. For example, at no point does the Bent *et al.* reference disclose a frequency of direct mucoadministration that is effective to reduce or eliminate non-invasive fungus-induced rhinosinusitis. Thus, given these deficiencies, Applicant respectfully requests withdrawal of the rejection of claims 1-9, 13-18, 20, 21, 30, 40, 46, and 47 under 35 U.S.C. §102(a).

Rejections under 35 U.S.C. §102(b)

The Examiner rejected claims 1-9, 13, 16, 20, 22-24, 30-32, 34-36, 40-42, 46, and 47 under 35 U.S.C. §102(b) as being anticipated by Bassiouny *et al.* (*J. Laryngol. Otol.* 96:215-228 (1982)). Specifically, the Examiner stated that the Bassiouny *et al.* reference teaches (1) the treatment of fungal nasal sinusitis using paranasal irrigation and daily instillation of 20 mL of clotrimazole solution, and (2) a bi-weekly antral washout followed by instillation of 20 mL clotrimazole solution for four consecutive weeks. In addition, the Examiner stated that the Bassiouny *et al.* reference "teaches that identification and proper diagnosis of the patient is important and teaches the method thereof."

Applicant respectfully disagrees. The term "fungal sinusitis" encompasses several distinct diseases. As set forth in the 1996 review article cited by the Examiner (Morpeth *et al.*,

Annals Allergy Asthma Immunol. 76:128-140 (1996)), a "classification system has evolved, essentially dividing fungal sinusitis into four primary categories: (1) acute/fulminant, (2) chronic/indolent, (3) fungus ball, and (4) allergic fungal sinusitis." This review article also indicates that each "subtype has unique immunologic, pathologic, and clinical features" and the "treatment and prognosis of fungal sinusitis varies significantly among the four different categories." The term "non-invasive fungus-induced rhinosinusitis" as used in the present claims includes allergic fungal sinusitis. See, e.g., page 27, lines 24-25 of Applicant's specification. The term "non-invasive fungus-induced rhinosinusitis" does not include acute/fulminant fungal sinusitis, chronic/indolent fungal sinusitis, or fungus balls. Thus, a reference simply disclosing the treatment of acute/fulminant fungal sinusitis, chronic/indolent fungal sinusitis, or fungus balls does not disclose the treatment of non-invasive fungus-induced rhinosinusitis.

The Bassiouny *et al.* reference discloses six case reports. In each case, the patient had either chronic/indolent fungal sinusitis or fungus balls as opposed to non-invasive fungus-induced rhinosinusitis. In fact, a person having ordinary skill in the art at the time Applicant filed the present application would have appreciated that each patient disclosed in the Bassiouny *et al.* reference had either chronic/indolent fungal sinusitis or fungus balls as opposed to non-invasive fungus-induced rhinosinusitis for the following reasons. First, chronic/indolent fungal sinusitis is characterized by tissue invasion. See, Table I of the Morpeth *et al.* review article. Figure 6 of the Bassiouny *et al.* reference shows fungus "invading the submucosa." Second, the work disclosed in the Bassiouny *et al.* reference was done at a hospital in Saudi Arabia. It was well known that chronic/indolent fungal sinusitis is endemic in that region of the world. For example, the Morpeth *et al.* review article specifically states that chronic/indolent fungal sinusitis "is endemic in areas such as the Sudan and northern India . . . ." See, page 131 of the Morpeth *et al.* review article. Third, fungus balls consist of tightly packed fungi and have a clay-like appearance. See, page 131 of the Morpeth *et al.* review article. The presence of concretions as shown in the figures of the Bassiouny *et al.* reference is consistent with the existence of fungus balls. See, e.g., Figure 2 and 3 of the Bassiouny *et al.* reference. Fourth, a research article about fungal diseases of the sinuses cites the Bassiouny *et al.* reference stating that "[s]ubsequent reports have illustrated a range of diseases occurring in the sinuses, ranging from the common allergic rhinitis to fungal antigens, to allergic *Aspergillus* sinusitis,[3-5] through fungus balls,[6] and

invasive and fulminant fungal sinusitis capable of causing death within hours to days.[7-9]" See, page 1012 of Corey *et al.*, *Otol. Head Neck Surg.*, 103:1012-1015 (1990). In this article, the Bassiouny *et al.* reference is listed as reference number 6. For the Examiner's convenience, a copy of the Corey *et al.* reference is submitted with the accompanying Information Disclosure Statement. Thus, a person having ordinary skill in the art at the time Applicant filed the present application would have understood that the Bassiouny *et al.* reference simply discloses an attempted treatment of diseases other than non-invasive fungus-induced rhinosinusitis. Since the Bassiouny *et al.* reference fails to disclose the treatment of non-invasive fungus-induced rhinosinusitis, the Bassiouny *et al.* reference does not anticipate the presently claimed invention.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1-9, 13, 16, 20, 22-24, 30-32, 34-36, 40-42, 46, and 47 under 35 U.S.C. §102(b).

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 12, 19, 22-29, 31-39, 41-45, and 48-59 under 35 U.S.C. §103(a) as being unpatentable over Bent *et al.* (Laryngoscope 106:1331-1334 (1996)). Specifically, the Examiner stated that the Bent *et al.* reference teaches (1) the use of topical antifungal irrigation in the treatment of allergic fungal sinusitis, and (2) a therapeutic antifungal solution of 1 mg/mL ketoconazole. In addition, the Examiner stated that the Bent *et al.* reference "teaches that proper identification of the disease is essential and the method thereof." The Examiner acknowledges that the Bent *et al.* reference does not teach (1) the recited use of a macrolide antifungal agent, (2) the recited use of itraconazole, (3) the recited effective amounts, (4) the recited effective frequencies of treatment, (5) the recited effective durations of treatment, (6) the recited use of a second formulation, (7) the recited preventive treatment, (8) the recited article of manufacture, (9) the recited formulation, or (10) the recited method of manufacture. In an attempt to overcome the deficiencies of the Bent *et al.* reference, the Examiner stated:

> One of ordinary skill in the art would have found it obvious to modify the primary reference by employing the effective amounts, the frequency or duration of treatment herein, using the second formulation herein, employing the claimed method in preventive treatment , and employing such antifungal compounds in the article of manufacture of composition herein.

A person of ordinary skill in the art would have been motivated to make these modifications because; any known antifungal agent would be expected to be similarly useful. Optimization of the amount to be administered or dosage of an active agent is considered within the skill of the artisan. Futher the employment of a second formulation containing topical steroid is motivated since these agents are known to be useful to treat allergic fungus sinusitis. See page 1331, column 2 in Bent. The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungus sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would be expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents is known in the treatment of allergic fungus sinusitis. See e.g., page 1333, column 1 in Bent. Finally, the method of making a composition by mixing or combining ingredients is considered prima facie obvious.

Applicant respectfully disagrees. Again, as established above, at no point does the Bent *et al.* reference disclose the successful treatment of allergic fungal sinusitis. The authors of the Bent *et al.* reference specifically state that they "attempted intraoperative and postoperative topical irrigations with fluconazole without success." Thus, a person having ordinary skill in the art reading the Bent *et al.* reference would have had no reasonable expectation of success in treating allergic fungal sinusitis. In fact, a person having ordinary skill in the art would have reasonably expected that nasal irrigations with an antifungal agent would have been an unsuccessful treatment for allergic fungal sinusitis. In light of the deficiencies in the Bent *et al.* reference, Applicant respectfully requests withdrawal of the rejection of claims 12, 19, 22-29, 31-39, 41-45, and 48-59 under 35 U.S.C. §103(a).

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 12, 14, 15, 17-19, 21, 25-29, 33, 37-39, 43-45, and 48-59 under 35 U.S.C. §103(a) as being unpatentable over Bassiouny *et al.* (*J. Laryngol. Otol.* 96:215-228 (1982)) and Morpeth *et al.* (*Annals Allergy Asthma Immunol.*, 76:128-140 (1996)). Specifically, the Examiner stated that the Bassiouny *et al.* reference teaches (1) the treatment of fungal nasal sinusitis using paranasal irrigation and daily instillation of 20 mL of clotrimazole solution, and (2) a bi-weekly antral washout followed by instillation of 20 mL clotrimazole solution for four consecutive weeks. The Examiner also stated that the Bassiouny *et al.* reference "teaches that identification and proper diagnosis of the patient is important and teaches

the method thereof." In addition, the Examiner stated that the Morpeth *et al.* reference teaches the use of saline irrigation followed by topical intranasal administration of corticosteroids and antifungal agents. The Examiner acknowledges that the references do not teach (1) the recited employment of macrolide, sterol inhibitor, and cell wall interpolator antifungals, (2) the recited effective amounts, (3) the recited effective frequencies, (4) the effective durations, (5) the recited preventive treatment, (6) the recited article of manufacture, (7) the recited formulation, and (8) the recited method of manufacture. In an attempt to overcome the deficiencies of the Bassiouny *et al.* and Morpeth *et al.* references, the Examiner stated:

> A person of ordinary skill in the art would have been motivated to make these modifications because; any antifungal agents would be expected to be similarly useful. The employment of a composition which is known to be useful in the treatment of a disorder such as allergic fungus sinusitis, in the prevention of the same disorder, is considered clearly obvious as therapeutic effects would be expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents is known in the treatment of allergic fungus sinusitis. See e.g., page 1333, column 1 in Bent. Finally, the method of making a composition by mixing or combining ingredients is considered prima facie obvious.

Applicant respectfully disagrees. As explained above, the Bassiouny *et al.* reference discloses an attempted treatment of diseases other than non-invasive fungus-induced rhinosinusitis. Thus, a person having ordinary skill in the art reading the Bassiouny *et al.* reference would have understood that the Bassiouny *et al.* reference provides little, if any, useful information for the treatment of non-invasive fungus-induced rhinosinusitis. In fact, after reading the Bassiouny *et al.* reference, a person of ordinary skill in the art would not have been motivated to treat non-invasive fungus-induced rhinosinusitis but rather would have been motivated to treat either chronic/indolent fungal sinusitis or fungus balls. Moreover, the Bassiouny *et al.* reference fails to provide a reasonable expectation of success in treating non-invasive fungus-induced rhinosinusitis as presently claimed.

The Morpeth *et al.* reference does not overcome the deficiencies of the Bassiouny *et al.* reference. At no point does the Morpeth *et al.* reference disclose the presently claimed method for treating non-invasive fungus-induced rhinosinusitis. In addition, at no point does the Morpeth *et al.* reference suggest using either chronic/indolent fungal sinusitis or fungus ball

treatments to treat a non-invasive fungus-induced rhinosinusitis condition such as allergic fungal sinusitis. Instead, the Morpeth *et al.* reference highlights the distinct nature of the four general categories of fungal sinusitis and specifically states that their treatment and prognosis vary significantly. Thus, the combination of the Bassiouny *et al.* and Morpeth *et al.* references fails to render the presently claimed treatment of non-invasive fungus-induced rhinosinusitis obvious. In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 12, 14, 15, 17-19, 21, 25-29, 33, 37-39, 43-45, and 48-59 under 35 U.S.C. §103(a).

CONCLUSION

Applicant submits that claims 1-9, 12-40, 42-46, 48-59, and 70-72 are in condition for allowance, which action is requested. Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: May 23, 2000

J. Patrick Finn III, Ph.D.
Reg. No. 44,109

Fish & Richardson P.C., P.A.
60 South Sixth Street, Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

60009035.doc

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

AUG 18

Docketed By Practice Systems
Action Code:
Base Date:
Due Date:
Deadline:
Initials:

Docketed By Practice Systems
Action Code:
Base Date:
Due Date:
Deadline:
Initials:

Docketed By Billing Secretary
Due Date:
Deadline:
Initials:

PTO-90C (Rev. 2/95)

2 - Mail Copy

Office Action Summary	Application No.	Applicant(s)	
	09/177,164	PONIKAU, JENS	
	Examiner	Art Unit	
	Shengjun Wang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *05 June 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40,42-46,48-59 and 70-72* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12-40,42-46,48-59 and 70-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Receipt of the amendment and remarks submitted June 5, 2000 is acknowledged.

Claim Rejections 35 U.S.C. – 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-9, 13-18, 20-21, 30, 40 and 46 are rejected under 35 U.S.C. 102(a) as being anticipated by Bent III et al. (of record) for reasons stated in the prior office action.

3. Claims 1-9, 13, 16, 20, 22-24, 30-32, 34-36, 40, 42 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Bassiouny et al (of record) for reasons stated in the prior office action.

Claim Rejection 35 U.S.C. – 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 12, 19, 22-29, 31-39, 42-45, 48-59 and 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bent III et al. for essentially the same reasons stated in the prior office action. Particularly regarding newly added claims 70-72, a method known to be useful in the treatment of sinusitis in mammals would have been reasonably expected to be useful to treat

the sinusitis in the mammal without regard to any previous nasal surgery, absent evidence to the contrary.

6. Claims 12, 14-15, 17-19, 21, 25-29, 33, 37-39, 43-45, 48-59 and 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bassiouny et al. (of record) and Morpeth et al (of record) for essentially the same reasons stated in the prior office action. Particularly regarding newly added claims 70-72, a method known to be useful in the treatment of sinusitis in mammals would have been reasonably expected to be useful to treat the sinusitis in the mammal without regard to any previous nasal surgery, absent evidence to the contrary.

7. Applicants' remarks submitted June 5, 2000 have been fully considered but are not persuasive for reasons discussed below.

8. Regarding the remarks that Bent III et al does not disclose a successful treatment of allergic fungal sinusitis and the direct mucoadministration in an amount, at a frequency, and for a duration effective to reduce or eliminate non-invasive fungus-induced rhinosinsitis, note that the irrigation of nasal mucous membranes is considered a direct mucoadministration. Such irrigation is known to be successful in reducing or treating sinusitis. See the conclusion on page 1334 in Bent III. Further, since Bent III's method is effective, the amounts of the pharmaceutical composition, the frequency and duration for administering the pharmaceutical composition in the method of Bent III are considered effective. Applicants' citation of a sentence from Bent III et al., "attempted intraoperative and postoperative topical irrigations with fluconazole without success." (at column 1 of page 1333) as a basis to assert that there was no reasonable expectation of success for the claimed method in view of this reference has been considered but is not persuasive. Note that the full sentence from which the above excerpt was taken is, "In the early

phases of this study we attempted intraoperative and postoperative topical irrigations with fluconazole without success." See again page 1333, column 1. Bent III et al. in their study, have optimized the earlier to improve the treatment results. See, page 1333, left-hand column, the last paragraph.

9. Applicants' remarks regarding Bassiouny et al. not teaching the treatment of "non-invasive fungus-induced sinusitis" as claimed in the instant application have been fully considered but are not persuasive. Applicants' statement appears to be based on that the cases disclosed by Bassiouny et al. which are either chronic/indolent fungal sinusitis or fungus balls and whereas the claims of instant application recite "non-invasive fungus-induced sinusitis," a condition which includes allergic fungal sinusitis. However, the generally accepted definition of "non-invasive fungus-induced sinusitis" includes allergic fungal sinusitis and fungus balls. See table 1 on page 129 in Morpeth et al. The specification of the instant application does not particularly define "non-invasive fungus-induced sinusitis" exclusively as allergic fungal sinusitis. See, page 27, lines 24-25. Therefore "non-invasive fungus-induced sinusitis" as defined in the specification includes the particular fungal conditions discussed in Bossiouny.

Nothing unobvious is seen for the claimed invention.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang, Ph.D. whose telephone number is (703) 308-4554. The examiner can normally be reached on Monday-Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, J.D., can be reached on (703) 308-4612. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Shengjun Wang

AU 1617

August 4, 2000

MINNA MOEZIE
PRIMARY EXAMINER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Jens Ponikau
Serial No. : 09/177,164
Filed : October 22, 1998
Title : METHODS AND MATERIALS FOR TREATING AND PREVENTING INFLAMMATION OF MUCOSAL TISSUE

Art Unit : 1617
Examiner : Shengjun Wang

BOX CPA
Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination and in response to the action mailed August 15, 2000, please amend the application as follows:

In the Claims

Please amend claims 1 and 46 as follows:

1. (Once Amended) A method for treating a mammal having non-invasive fungus-induced rhinosinusitis comprising the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent.

46. (Once Amended) A method for treating a mammal having a non-invasive fungus-induced rhinosinusitis comprising the presence of allergic mucus, said method comprising the steps of:

a) identifying said mammal, and

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December 15, 2000
Date of Deposit


Signature

Vince Defante
Typed or Printed Name of Person Signing Certificate

b) directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent.

Please add new claims 73-188 as follows:

--73. The method of claim 1, wherein said non-invasive fungus-induced rhinosinusitis comprises the presence of a polyp.

74. The method of claim 1, wherein said non-invasive fungus-induced rhinosinusitis comprises eosinophilia.

75. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis comprising the presence of a polyp, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent.

76. The method of claim 75, wherein said mammal is a human.

77. The method of claim 75, wherein said formulation is in a liquid or aerosol.

78. The method of claim 75, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

79. The method of claim 75, wherein said antifungal agent comprises a macrolide.

80. The method of claim 75, wherein said antifungal agent comprises an azole.

81. The method of claim 75, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, voriconazole, flucytosine, miconazole, fluconazole, griseofulvin, clotrimazole, econazole, terconazole, butoconazole, oxiconazole, sulconazole, ciclopirox olamine, haloprogin, tolnaftate, naftifine, terbinafine hydrochloride, morpholines, nystatin, natamycin, butenafine, undecylenic acid, Whitefield's ointment, propionic acid, and caprylic acid.

82. The method of claim 75, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

83. The method of claim 75, wherein said antifungal agent comprises amphotericin B.

84. The method of claim 75, wherein said antifungal agent comprises itraconazole.

85. The method of claim 75, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

86. The method of claim 85, wherein said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per liter.

87. The method of claim 86, wherein said effective amount comprises about 0.01 mL to about 1 L of said formulation per nostril of said mammal.

88. The method of claim 86, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

89. The method of claim 85, wherein said formulation comprises about 1 ng to about 500 mg of said antifungal agent per liter.

90. The method of claim 75, wherein said formulation comprises a plurality of antifungal agents.

91. The method of claim 75, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

92. The method of claim 75, wherein said effective frequency of said direct mucoadministration is from about four times a day to about once every other week.

93. The method of claim 75, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

94. The method of claim 75, wherein said effective duration is greater than about 30 days.

95. The method of claim 75, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

96. The method of claim 95, wherein said mammal had a nasal surgery before said mucoadministration.

97. The method of claim 95, wherein said mammal was nasal surgery-free before said mucoadministration.

98. The method of claim 75, said method comprising, after said direct mucoadministration, prophylactically mucoadministering to said mammal a prophylactic formulation in an amount, at a frequency, and for a duration effective to prevent said non-invasive fungus-induced rhinosinusitis, said prophylactic formulation comprising an antifungal agent.

99. The method of claim 95, wherein said prophylactic mucoadministration comprises direct mucoadministration.

100. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis comprising the presence of a polyp, said method comprising:

a) identifying said mammal, and

b) directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent.

101. An article of manufacture, comprising packaging material and a formulation contained within said packaging material, wherein said formulation comprises an antifungal agent and wherein said packaging material comprises a label or package insert indicating that said formulation can be directly mucoadministered to at least a portion of the nasal-paranasal anatomy of a mammal having non-invasive fungus-induced rhinosinusitis in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis comprises the presence of a polyp.

102. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis comprising eosinophilia, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent.

103. The method of claim 102, wherein said mammal is a human.

104. The method of claim 102, wherein said mammal is nonatopic.

105. The method of claim 102, wherein said mammal is immunocompetent.

106. The method of claim 102, wherein said non-invasive fungus-induced rhinosinusitis comprises polyp formation or polypoid change.

107. The method of claim 102, wherein said non-invasive fungus-induced rhinosinusitis is chronic.

108. The method of claim 102, wherein said formulation is in a liquid or aerosol form.

109. The method of claim 102, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

110. The method of claim 102, wherein said antifungal agent comprises a macrolide.

111. The method of claim 102, wherein said antifungal agent comprises an azole.

112. The method of claim 102, wherein said antifungal agent interpolates fungal cell wall components.

113. The method of claim 102, wherein said antifungal agent comprises a sterol inhibitor.

114. The method of claim 102, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, voriconazole, flucytosine, miconazole, fluconazole, griseofulvin, clotrimazole, econazole, terconazole, butoconazole, oxiconazole, sulconazole, ciclopirox olamine, haloprogin, tolnaftate, naftifine, terbinafine hydrochloride, morpholines, nystatin, natamycin, butenafine, undecylenic acid, Whitefield's ointment, propionic acid, and caprylic acid.

115. The method of claim 102, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

116. The method of claim 102, wherein said antifungal agent comprises amphotericin B.

117. The method of claim 102, wherein said antifungal agent comprises itraconazole.

118. The method of claim 102, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

119. The method of claim 118, wherein said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per liter.

120. The method of claim 119, wherein said effective amount comprises about 0.01 mL to about 1 L of said formulation per nostril of said mammal.

121. The method of claim 119, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

122. The method of claim 119, wherein said effective amount comprises about 20 mL of said formulation per nostril of said mammal.

123. The method of claim 118, wherein said formulation comprises about 1 ng to about 500 mg of said antifungal agent per liter.

124. The method of claim 118, wherein said formulation comprises about 100 mg of said antifungal agent per liter.

125. The method of claim 102, wherein said formulation comprises a plurality of antifungal agents.

126. The method of claim 102, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

127. The method of claim 102, wherein said effective amount of said formulation comprises about 1 ng to about 500 mg of said antifungal agent per kg of body weight of said mammal.

128. The method of claim 102, wherein said effective amount of said formulation remains constant during said effective duration.

129. The method of claim 102, wherein said effective frequency of said direct mucoadministration is from about four times a day to about once every other week.

130. The method of claim 102, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

131. The method of claim 102, wherein said effective frequency of said direct mucoadministration is more frequent than once a day.

132. The method of claim 102, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

133. The method of claim 102, wherein said effective duration is greater than about 7 days.

134. The method of claim 102, wherein said effective duration is greater than about 14 days.

135. The method of claim 102, wherein said effective duration is greater than about 30 days.

136. The method of claim 102, wherein said effective duration is greater than about 60 days.

137. The method of claim 102, wherein said effective duration is greater than about 90 days.

138. The method of claim 102, wherein said formulation further comprises a compound selected from the group consisting of pharmaceutically acceptable aqueous vehicles, pharmaceutically acceptable solid vehicles, mucolytic agents, antibacterial agents, anti-inflammatory agents, immunosuppressants, dilators, vaso-constrictors, and steroids.

139. The method of claim 102, wherein said method further comprises administering to said mammal a second formulation, said second formulation comprising a compound selected from the group consisting of antifungal agents, pharmaceutically acceptable aqueous vehicles, pharmaceutically acceptable solid vehicles, mucolytic agents, antibacterial agents, anti-inflammatory agents, immunosuppressants, dilators, vaso-constrictors, and steroids.

140. The method of claim 102, said method comprising, after said direct mucoadministration, prophylactically mucoadministering to said mammal a prophylactic formulation in an amount, at a frequency, and for a duration effective to prevent said non-invasive fungus-induced rhinosinusitis, said prophylactic formulation comprising an antifungal agent.

141. The method of claim 140, wherein said prophylactic mucoadministration comprises direct mucoadministration.

142. The method of claim 102, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

143. The method of claim 142, wherein said mammal had a nasal surgery before said mucoadministration.

144. The method of claim 142, wherein said mammal was nasal surgery-free before said mucoadministration.

145. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis comprising eosinophilia, said method comprising:

a) identifying said mammal, and

b) directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent.

146. A method for prophylactically treating a mammal at risk for developing non-invasive fungus-induced rhinosinusitis comprising eosinophilia, said method comprising:

a) identifying said mammal, and

b) mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to prevent said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent.

147. An article of manufacture, comprising packaging material and a formulation contained within said packaging material, wherein said formulation comprises an antifungal agent and wherein said packaging material comprises a label or package insert indicating that said formulation can be directly mucoadministered to at least a portion of the nasal-paranasal anatomy of a mammal having non-invasive fungus-induced rhinosinusitis in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis comprises eosinophilia.

148. An article of manufacture, comprising packaging material and a formulation contained within said packaging material, wherein said formulation comprises an antifungal agent and wherein said packaging material comprises a label or package insert indicating that said formulation can be mucoadministered to at least a portion of the nasal-paranasal anatomy of a

mammal at risk for developing non-invasive fungus-induced rhinosinusitis in an amount, at a frequency, and for a duration effective to prevent said non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis comprises eosinophilia.

149. A method for treating a mammal having allergic fungal sinusitis, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said allergic fungal sinusitis, said formulation comprising an antifungal agent.

150. The method of claim 149, wherein said mammal is a human.

151. The method of claim 149, wherein said allergic fungal sinusitis comprises polyp formation or polypoid change.

152. The method of claim 149, wherein said formulation is in a liquid or aerosol form.

153. The method of claim 149, wherein said formulation is in a liquid or solid form.

154. The method of claim 149, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

155. The method of claim 149, wherein said antifungal agent comprises a macrolide.

156. The method of claim 149, wherein said antifungal agent comprises an azole.

157. The method of claim 149, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, voriconazole, flucytosine, miconazole, fluconazole, griseofulvin, clotrimazole, econazole, terconazole, butoconazole, oxiconazole, sulconazole, ciclopirox olamine, haloprogin, tolnaftate,

naftifine, terbinafine hydrochloride, morpholines, nystatin, natamycin, butenafine, undecylenic acid, Whitefield's ointment, propionic acid, and caprylic acid.

158. The method of claim 149, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

159. The method of claim 149, wherein said antifungal agent comprises amphotericin B.

160. The method of claim 149, wherein said antifungal agent comprises itraconazole.

161. The method of claim 149, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

162. The method of claim 161, wherein said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per liter.

163. The method of claim 162, wherein said effective amount comprises about 0.01 mL to about 1 L of said formulation per nostril of said mammal.

164. The method of claim 162, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

165. The method of claim 161, wherein said formulation comprises about 1 ng to about 500 mg of said antifungal agent per liter.

166. The method of claim 161, wherein said formulation comprises about 100 mg of said antifungal agent per liter.

167. The method of claim 149, wherein said formulation comprises a plurality of antifungal agents.

168. The method of claim 149, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

169. The method of claim 149, wherein said effective amount of said formulation comprises about 1 ng to about 500 mg of said antifungal agent per kg of body weight of said mammal.

170. The method of claim 149, wherein said effective amount of said formulation remains constant during said effective duration.

171. The method of claim 149, wherein said effective frequency of said direct mucoadministration is from about four times a day to about once every other week.

172. The method of claim 149, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

173. The method of claim 149, wherein said effective frequency of said direct mucoadministration is more frequent than once a day.

174. The method of claim 149, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

175. The method of claim 149, wherein said effective duration is greater than about 30 days.

176. The method of claim 149, wherein said effective duration is greater than about 90 days.

177. The method of claim 149, wherein said formulation further comprises a compound selected from the group consisting of pharmaceutically acceptable aqueous vehicles,

pharmaceutically acceptable solid vehicles, mucolytic agents, antibacterial agents, anti-inflammatory agents, immunosuppressants, dilators, vaso-constrictors, and steroids.

178. The method of claim 149, wherein said method further comprises administering to said mammal a second formulation, said second formulation comprising a compound selected from the group consisting of antifungal agents, pharmaceutically acceptable aqueous vehicles, pharmaceutically acceptable solid vehicles, mucolytic agents, antibacterial agents, anti-inflammatory agents, immunosuppressants, dilators, vaso-constrictors, and steroids.

179. The method of claim 149, said method comprising, after said direct mucoadministration, prophylactically mucoadministering to said mammal a prophylactic formulation in an amount, at a frequency, and for a duration effective to prevent said allergic fungal sinusitis, said prophylactic formulation comprising an antifungal agent.

180. The method of claim 179, wherein said prophylactic mucoadministration comprises direct mucoadministration.

181. The method of claim 149, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

182. The method of claim 181, wherein said mammal had a nasal surgery before said mucoadministration.

183. The method of claim 181, wherein said mammal was nasal surgery-free before said mucoadministration.

184. A method for prophylactically treating a mammal at risk for developing allergic fungal sinusitis, said method comprising mucoadministering to said mammal a formulation in an

amount, at a frequency, and for a duration effective to prevent said allergic fungal sinusitis, said formulation comprising an antifungal agent.

185. A method for treating a mammal having allergic fungal sinusitis, said method comprising:

a) identifying said mammal, and

b) directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said allergic fungal sinusitis, said formulation comprising an antifungal agent.

186. A method for prophylactically treating a mammal at risk for developing allergic fungal sinusitis, said method comprising:

a) identifying said mammal, and

b) mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to prevent said allergic fungal sinusitis, said formulation comprising an antifungal agent.

187. An article of manufacture, comprising packaging material and a formulation contained within said packaging material, wherein said formulation comprises an antifungal agent and wherein said packaging material comprises a label or package insert indicating that said formulation can be directly mucoadministered to at least a portion of the nasal-paranasal anatomy of a mammal having allergic fungal sinusitis in an amount, at a frequency, and for a duration effective to reduce or eliminate said allergic fungal sinusitis.

188. An article of manufacture, comprising packaging material and a formulation contained within said packaging material, wherein said formulation comprises an antifungal agent and wherein said packaging material comprises a label or package insert indicating that said formulation can be mucoadministered to at least a portion of the nasal-paranasal anatomy of a mammal at risk for developing allergic fungal sinusitis in an amount, at a frequency, and for a duration effective to prevent said allergic fungal sinusitis.--

REMARKS

The Examiner rejected claims 1-9, 12-40, 42-46, 48-59, and 70-72 and withdrew claims 10 and 11 from consideration. Claims 1 and 46 have been amended, and new claims 73-188 have been added herein. Thus, claims 1-40, 42-46, 48-59, and 70-188 are pending. The specification as filed provides support for these claim amendments and new claims. For example, page 58, lines 19-24 disclose that the patients had non-invasive fungus-induced rhinosinusitis with allergic mucus; page 59, lines 3-19 disclose the results of treating patients having non-invasive fungus-induced rhinosinusitis with polyps in the middle meatus (stage 2) or with polyps filling the nasal cavity (stage 3); page 66, lines 1-14 disclose the results of treating a patient having non-invasive fungus-induced rhinosinusitis with eosinophilia; and page 4, lines 8-10 disclose that non-invasive fungus-induced rhinosinusitis can be allergic fungal sinusitis (AFS). Thus, no new matter is added by these amendments. In light of the following remarks, Applicant respectfully requests reconsideration and allowance of claims 1-9, 12-40, 42-46, 48-59, and 70-188.

Withdrawn objections and rejections

Applicant acknowledges withdrawal of the Examiner's objections to claims 27, 40, 56, and 57. Applicant also acknowledges withdrawal of the Examiner's rejections of claims 3, 8, 40, 42, 45, 48, and 50 under 35 U.S.C. §112.

Telephonic Interviews

Applicant's agent thanks Examiner Wang for the courtesy of the telephonic interview on October 13, 2000 and Primary Examiner Travers for the courtesy of the telephonic interview on November 13, 2000. The substance of these telephonic interviews involved the issues and arguments presented herein.

Information Disclosure Statement

Applicant respectfully notes that an initialed copy of the PTO-1449 form filed May 23, 2000 has not been returned. Thus, Applicant respectfully requests return of an initialed copy.

For the Examiner's convenience, a copy of the PTO-1449 form filed May 23, 2000 is attached hereto. In addition, a copy of the listed reference can be resubmitted upon request.

Rejections under 35 U.S.C. §102(a)

The Examiner rejected claims 1-9, 13-18, 20, 21, 30, 40, and 46 under 35 U.S.C. §102(a) as being anticipated by Bent *et al.* (Laryngoscope 106:1331-1334 (1996)) for the reasons stated in the office action mailed February 29, 1999. In addition, the Examiner provided several remarks in response to Applicant's arguments filed May 23, 1999. First, citing to the conclusion on page 1334 of the Bent *et al.* reference, the Examiner stated that the irrigation of nasal mucus membranes "is known to be successful in reducing or treating sinusitis." Second, the Examiner stated that "since Bent III's method is effective, the amounts of the pharmaceutical composition, the frequency and duration for administering the pharmaceutical composition in the method of Bent III are considered effective." Third, the Examiner stated that Bent *et al.* "have optimized the earlier to improve the treatment results."

Applicant respectfully disagrees with the Examiner's characterization of the Bent *et al.* reference. First, the language in the conclusion section of the Bent *et al.* reference does not disclose that irrigating nasal mucus membranes with an antifungal agent is known to be successful in reducing or treating sinusitis as the Examiner contends. In fact, at no point does the Bent *et al.* reference disclose the successful use of an antifungal agent to treat allergic fungal sinusitis.

Second, the Examiner's premise that "Bent III's method is effective" is unfounded. Again, at no point does the Bent *et al.* reference disclose results indicating an effective antifungal treatment method. In fact, the only antifungal treatment results disclosed in the Bent *et al.* reference indicate that topical irrigations are unsuccessful. Specifically, the second sentence of the second complete paragraph on page 1333 of the Bent *et al.* reference states "[i]n the early phases of this study we attempted intraoperative and postoperative topical irrigations with fluconazole without success." Moreover, the third complete paragraph of the Bent *et al.* reference specifically states that "[a]ny clinical trial would require a standardized method of monitoring patient response to disease" and "one must depend on nasal examination to obtain legitimate information about disease status." Consequently, the authors of the Bent *et al.*

reference proposed an objective classification system to evaluate treatment effectiveness. The Bent *et al.* reference, however, fails to disclose any treatment data using this objective classification system. Thus, a person of ordinary skill in the art reading the Bent *et al.* reference would not have concluded that "Bent III's method is effective" as the Examiner contends.

Third, as discussed above, the Bent *et al.* reference does not disclose any successful treatment results, let alone the optimization of successful treatment results as the Examiner contends. Again, the only treatment results disclosed in the Bent *et al.* reference indicate that topical antifungal irrigations are unsuccessful.

In light of the above and the arguments of record, Applicant respectfully requests withdrawal of the rejection of claims 1-9, 13-18, 20, 21, 30, 40, and 46 under 35 U.S.C. §102(a).

Rejections under 35 U.S.C. §102(b)

The Examiner rejected claims 1-9, 13, 16, 20, 22-24, 30-32, 34-36, 40, 42, and 46 under 35 U.S.C. §102(b) as being anticipated by Bassiouny *et al.* (*J. Laryngol. Otol.* 96:215-228 (1982)) for the reasons stated in the office action mailed February 29, 1999. In addition, the Examiner provided several remarks in response to Applicant's arguments filed May 23, 1999. Specifically, the Examiner stated that (1) the generally accepted definition of non-invasive fungus-induced sinusitis includes allergic fungal sinusitis and fungus balls, and (2) non-invasive fungus-induced sinusitis as defined in the specification includes the particular fungal conditions discussed in the Bassiouny *et al.* reference.

Applicant respectfully disagrees. As indicated in Applicant's response filed May 23, 1999, the term "non-invasive fungus-induced rhinosinusitis" does not include fungus balls, and a person having ordinary skill in the art at the time Applicant filed the present application would have appreciated that each patient disclosed in the Bassiouny *et al.* reference had either chronic/indolent fungal sinusitis or fungus balls as opposed to non-invasive fungus-induced rhinosinusitis. Thus, the Bassiouny *et al.* reference does not disclose the treatment of non-invasive fungus-induced rhinosinusitis.

To facilitate prosecution and explicitly set forth that the term "non-invasive fungus-induced rhinosinusitis" does not include fungus balls, claims 1 and 46 have been amended to recite non-invasive fungus-induced rhinosinusitis comprising the presence of allergic mucus. As

set forth on page 24, lines 23-25 of Applicant's specification, allergic mucus is "mucus that contains evidence of eosinophil presence." At no point does the Bassiouny *et al.* reference disclose treating any condition containing allergic mucus. In addition, the Morpeth *et al.* review article cited by the Examiner specifically states that "the lack of eosinophils in the mucus of these patients differentiates this condition [fungus balls] from allergic fungal sinusitis." See, the last sentence on page 131 of the Morpeth *et al.* review article. Thus, the Bassiouny *et al.* reference does not disclose the treatment of non-invasive fungus-induced rhinosinusitis as presently claimed.

In light of the above and the arguments of record, Applicant respectfully requests withdrawal of the rejection of claims 1-9, 13, 16, 20, 22-24, 30-32, 34-36, 40, 42, and 46 under 35 U.S.C. §102(b).

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 12, 19, 22-29, 31-39, 42-45, 48-59, and 70-72 under 35 U.S.C. §103(a) as being unpatentable over Bent *et al.* (Laryngoscope 106:1331-1334 (1996)) for essentially the same reasons stated in the office action mailed February 29, 1999. In addition, with respect to new claims 70-72, the Examiner stated that "a method known to be useful in the treatment of sinusitis in mammals would have been reasonably expected to be useful to treat the sinusitis in the mammal without regard to any previous nasal surgery, absent evidence to the contrary."

Applicant respectfully disagrees with the Examiner's characterization of the Bent *et al.* reference. At no point does the Bent *et al.* reference disclose the successful treatment of allergic fungal sinusitis. In fact, the only treatment results disclosed in the Bent *et al.* reference indicate that antifungal irrigations are unsuccessful. Thus, a person having ordinary skill in the art reading the Bent *et al.* reference would have had no reasonable expectation of success in treating allergic fungal sinusitis.

In addition, at no point does the Bent *et al.* reference teach or suggest the antifungal formulations recited in claims 51-58 or the method of making an antifungal formulation recited in claim 59. For example, the Bent *et al.* reference never mentions an antifungal formulation having a flavoring or an itraconazole concentration as presently claimed. For a *prima facie* case

of obviousness, the cited reference or combination of cited references must teach or suggest all the claim limitations. See, MPEP §2142. The Bent *et al.* reference fails to teach or suggest all the claim limitations.

In light of the deficiencies in the Bent *et al.* reference, Applicant respectfully requests withdrawal of the rejection of claims 12, 19, 22-29, 31-39, 42-45, 48-59, and 70-72 under 35 U.S.C. §103(a).

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 12, 14, 15, 17-19, 21, 25-29, 33, 37-39, 43-45, 48-59, and 70-72 under 35 U.S.C. §103(a) as being unpatentable over Bassiouny *et al.* (*J. Laryngol. Otol.* 96:215-228 (1982)) and Morpeth *et al.* (*Annals Allergy Asthma Immunol.*, 76:128-140 (1996)) for essentially the same reasons stated in the office action mailed February 29, 1999. In addition, with respect to new claims 70-72, the Examiner stated that "a method known to be useful in the treatment of sinusitis in mammals would have been reasonably expected to be useful to treat the sinusitis in the mammal without regard to any previous nasal surgery, absent evidence to the contrary."

Applicant respectfully disagrees. As explained in Applicant's arguments filed May 23, 1999, the Bassiouny *et al.* reference discloses an attempted treatment of diseases other than non-invasive fungus-induced rhinosinusitis, and the Morpeth *et al.* reference does not overcome the deficiencies of the Bassiouny *et al.* reference. To facilitate prosecution, claims 1 and 46 have been amended to recite non-invasive fungus-induced rhinosinusitis comprising the presence of allergic mucus. At no point does the combination of the Bassiouny *et al.* and Morpeth *et al.* references teach or suggest treating any condition containing allergic mucus as presently claimed. Thus, the cited references fail to render the presently claimed obvious.

In addition, at no point do the Bassiouny *et al.* and Morpeth *et al.* references teach or suggest the antifungal formulations recited in claims 51-58 or the method of making an antifungal formulation recited in claim 59. In fact, neither cited reference mentions an antifungal formulation having a flavoring or an itraconazole concentration as presently claimed. Again, for a *prima facie* case of obviousness, the cited reference or combination of cited references must

teach or suggest all the claim limitations. See, MPEP §2142. The Bassiouny *et al.* and Morpeth *et al.* references fail to teach or suggest all the claim limitations.

In light of these deficiencies and the arguments of record, Applicant respectfully requests withdrawal of the rejection of claims 12, 14, 15, 17-19, 21, 25-29, 33, 37-39, 43-45, 48-59, and 70-72 under 35 U.S.C. §103(a).

CONCLUSION

Applicant submits that claims 1-40, 42-46, 48-59, and 70-188 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned agent at the telephone number below if such will advance prosecution of this application. Filed herewith is a check in payment of the excess claims fees required by the above amendments. The Assistant Commissioner is authorized to charge any other fees or credit any overpayments to Deposit Account No. 06-1050.

Respectfully submitted,

Date: December 15, 2000

J. Patrick Finn III, Ph.D.
Reg. No. 44,109

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
[illegible]	[illegible]	[illegible]	[illegible]

EXAMINER	
ART UNIT	PAPER NUMBER

MAR 19 2001

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Docketed By Practice Systems
Action Code: Response to OA
Base Date: 3/13/01
Due Date: 6/13/01
Deadline: 9/13/01
Initials: JMeaney

Docketed By Billing Secretary
Due Date: 6/13/01
Deadline: 9/13/01
Initials: DAS DVB

PTO-90C (Rev. 2/95)
*U S. GPO: 2000-473-000/44602

2 - Mail Copy

Office Action Summary	Application No.	Applicant(s)	
	09/177,164	PONIKAU, JENS	
	Examiner	Art Unit	
	Shengjun Wang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b)

Status

1)☒ Responsive to communication(s) filed on *15 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40,42-46,48-59 and 70-188* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12-40,42-46,48-59 and 70-188* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *23* .
18) ☒ Interview Summary (PTO-413) Paper No(s). *19* .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. The request filed on December 15, 2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/177,164 is acceptable and a CPA has been established. An action on the CPA follows.

Applicants' election in the parent application is presumed to carry over to the instant CPA since applicants have not indicated a contrary intention. Therefore, claims10 and 11 are withdrawn from further consideration as drawn to non-elected species.

Claim Rejections 35 U.S.C. § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-9, 12-40, 42-46, 48, 70-148 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 1, 46, 73-75, 101, 102, 106, 145-148 and 151 recite "...non-invasive fungus-induced rhinosinusitis comprising the presence of allergic mucus (or polyp, eosinophilia)..." The sentence is confusing in that it is unclear whether the presence of the said materials (allergic mucus or polyp, eosinophilia) is a symptom of the rhinosinusitis or the materials are added or obtained by the host. If applicants' intention is the former, following phrase may be considered: "... non-invasive fungus-induced rhinosinusitis, wherein the rhinosinusitis is accompanied with the presence of allergic mucus (or polyp, eosinophilia)..." The claims are indefinite as to how the rhinosinusitis would comprise "allergic mucus (or polyp, eosinophilia)."

Claim Rejections 35 U.S.C. – 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-9, 13-18, 20-21, 30, 40 and 46, 73-78, 80-85, 100, 149-154, 156-161184-185 are rejected under 35 U.S.C. 102(a) as being anticipated by Bent III et al. (AA, IDS, August 24, 1999) and Bent III et al. Allergy and Asthma Proc. (AE, IDS July 11, 2000).

3. Bent teaches the use of topical antifungal irrigation in the treatment of allergic fungal sinusitis in human. The antifungal agents are amphortericin B and/or ketoconazole. See, particularly, page 1331, the second column. The discussion on page 1333, second column and the conclusion on page 1334. Bent also teaches a therapeutic antifungal solution of 1mg/mL ketoconazole. See, particularly, page 1333, column 2, second paragraph. Bent III et al. Allergy and Asthma Proc. Teaches that allergic fungal sinusitis inherently process the characteristics including the presence of polyp and allergic mucus. See, particularly, the abstract, page 260, the last paragraph bridging to page 261.

Claim Rejections 35 U.S.C. § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-9, 12-40, 42-46, 48-59 and 70-188 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bent III et al. (AA, IDS, August 24, 1999) and Bent III et al. Allergy and Asthma Proc. (AE, IDS July 11, 2000) in view of Cody et al. (AM, IDS March 16, 1999)

4. Bent teaches the use of topical antifungal irrigation in the treatment of allergic fungal sinusitis in human. The antifungal agents are amphortericin B and/or ketoconazole. See, particularly, page 1331, the second column. The discussion on page 1333, second column and the conclusion on page 1334. Bent also teaches a therapeutic antifungal solution of 1mg/mL ketoconazole. See, particularly, page 1333, column 2, second paragraph. Bent III et al. Allergy and Asthma Proc. Teaches that allergic fungal sinusitis inherently process the characteristics including the presence of polyp and allergic mucus. See, particularly, the abstract, page 260, the last paragraph bridging to page 261. Bent III et al. Allergy and Asthma Proc. further teach the usefulness of topical steroid for the AFS. See, particularly, table III on page 266.

5. The cited reference do not teach expressly the non-invasive fungal-induced sinusitis is with presence of eosinophilia, or the particular formulation, duration of time, or the employment with other known antifungal agent, such as macrolid, or the combination with steroids.

6. However, Cody teaches that most of AFS patient is with eosinophilia and, as mentioned above, steroid is known to be useful for the treatment of AFS.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the method of Bent for treatment of

AFS patient including those with eosinophilia, or to employ the particular formulation herein with the said amount and duration.

A person of ordinary skill in the art would have been motivated to employ the method of Bent for treatment of AFS patient including those with eosinophilia, or to employ the particular formulation herein with the said amount and duration because the method is generally known to be useful for treatment of AFS and most of AFS are known to be with the presence eosinophilia. The optimization of a formulation of a known pharmaceutics agent and its administration amount and duration is considered within the skill of artisan, absent evidence to the contrary. The employment of the second ingredient, which is known to be useful for the same purpose is seen to be obvious. It is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus, the claimed invention which is a combination of two known germicides sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069.

The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis. See, e.g., page 1333, column 1, in Bent. Finally, the method of making a composition by mixing or combining ingredients is considered prima facie obvious.

7. Claims 1-9, 12-40, 42-46, 48-59 and 70-188 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cody et al. (AM, IDS March 16, 1999) in view of Bent III et al. Allergy and Asthma Proc. (AE, IDS July 11, 2000).

8. Cody et al. teaches the general methods for treatment of AFS. The methods including nasal administration of antifungal agents or steroids. See, particularly, the treatment on page 1078 and table V on page 1079.

Cody et al. does not teach expressly the particular regimen or the particular administration time and duration herein. However, optimization of such results-effecting parameters is considered within the skill of artisan as discussed above. A person of ordinary skill in the art would have been motivated to employ well-known antifungal agents, including azole or mocrolid compounds, optionally in combination with steroid, for treatment of AFS. The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis. Finally, the method of making a composition by mixing or combining ingredients is considered prima facie obvious.

9. Claims 75-148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsushima et al. (DB, IDS March 16, 1999) and Torpoco (Medline Abstract, AN 76164567) in view of deShazo (AR IDS July 11, 2000).

10. Tsushima et al. teaches a method for treating fungus ball, a known non-invasive fungus-induced disorder. The method comprising topically administration of antifungal agents such as amphotericin B or fluconazole. Torpoco teach that fungus ball is known to be with eosinophilia. See the abstract.

Tsushima et al. does not teach expressly the particular regimen or the particular administration time and duration herein and the disorder is fungus ball sinusitis. However, a person of ordinary skill in the art would have been motivated to employ the method for treatment of non-invasive fungus-induced sinusitis (fungus ball) because the method is known to be useful against fungus ball. Further, deShazo teaches that mycetoma (fungus ball sinusitis) may have presence of polyps. See, particularly the abstract. Further, optimization of such results-effecting parameters is considered within the skill of artisan as discussed above. A person of ordinary skill in the art would have been motivated to employ well-known antifungal agents, including azole or mocrolid compounds, optionally in combination with steroid, for treatment of AFS. The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis. Finally, the method of making a composition by mixing or combining ingredients is considered prima facie obvious.

Applicants' remarks and amendments submitted December 15, 2000 have been fully considered, but are not persuasive for reasons discussed below.

Regarding the remarks that the term "non-invasive fungus-induced rhinosinusitis" does not including fungus ball", note that Morpeth reference (of record) clearly indicate that fungus ball is a non-invasive. See the introduction part and table 1 in Morphet.

Regarding the remarks that the Bent reference does not teaches successful treatment of AFS, note that the claimed invention is directed to a method of treatment of a disorder Any method reducing the disorder would be considered a treatment. Bent's has shown the benefit of the method. Therefore, the method is considered to be a treatment.

Regarding the addition of the non-essential ingredient, such as flavoring, carrier, surfactant, into a therapeutical regimen, is considered an optimization of the regimen which is within the skill of the artisan as discussed above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang, Ph.D. whose telephone number is (703) 308-4554. The examiner can normally be reached on Monday-Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, J.D., can be reached on (703) 308-4612. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Shengjun Wang

AU 1617

March 9, 2001

RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200

Interview Summary	Application No.	Applicant(s)	
	09/177,164	PONIKAU, JENS	
	Examiner	Art Unit	
	Shengjun Wang	1617	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Shengjun Wang*. (3)_____.

(2) *Patrick Finn*. (4)_____.

Date of Interview: *13 October 2000* .

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: .

Claim(s) discussed: *All* .

Identification of prior art discussed: *Bent et al. Bassiouny et al., and Morpeth et al.* .

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *See Continuation Sheet* .

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

i)☐ It is not necessary for applicant to provide a separate record of the substance of the interview(if box is checked).

Unless the paragraph above has been checked, THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

S. Wang
Examiner's signature, if required

Su. .ary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check the appropriate box at the bottom of the Form which informs the applicant that the submission of a separate record of the substance of the interview as a supplement to the Form is not required.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: The applicants' agent indicates that fungus ball is diffferent from allergic fungal sinusitis as indicated by Morpheth reference. Applicants will amend the claims to particularly direct the claimed method for treatment of allergic fungal sinusitis. Applicants' agent argue that Bent's reference does not teach or suggest the claimed invention. Bent does not present any succesful clinical data for treatment of fungal sinusitis. The statement page 1333 to 1334 is merely speculation which requires clinical trial for further support. Applicants will write the argument in the respon to the prior office action. The examiner indicate that the amendment and response will be fully considered when received.

L8 ANSWER 12 OF 14 MEDLINE
ACCESSION NUMBER: 76164576 MEDLINE
DOCUMENT NUMBER: 76164576
TITLE: Aspergilloma within a malignant pulmonary cavity.
AUTHOR: Torpoco J O; Yousuffuddin M; Pate J W
SOURCE: CHEST, (1976 Apr) 69 (4) 561-3.
Journal code: D1C. ISSN: 0012-3692.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 197608

AB The simultaneous appearance of both bronchogenic carcinoma and aspergilloma with the typical radiographic appearance of a **mycetoma** emphasizes the importance of consistent suspicion for malignancy in any pulmonary lesion. This is apparently the first reported case in which allergic phenomena (asthma-like symptoms and **eosinophilia**) are associated with an aspergilloma occurring within a cavitary bronchogenic carcinoma.

8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Jens Ponikau
Serial No. : 09/177,164
Filed : October 22, 1998
Title : METHODS AND MATERIALS FOR TREATING AND PREVENTING INFLAMMATION OF MUCOSAL TISSUE

Art Unit : 1617
Examiner : S. Wang

Commissioner for Patents
Washington, D.C. 20231

RESPONSE

In response to the action mailed March 13, 2001, please amend the application as follows.

In the claims:

Please cancel claims 1-40, 42-46, 48-59, and 70-188 without prejudice.

Please add new claims 189-246 as follows.

--189. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan, said formulation comprising an antifungal agent.

190. The method of claim 189, wherein said mammal is a human.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

Date of Deposit

Signature

Typed or Printed Name of Person Signing Certificate

191. The method of claim 189, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

192. The method of claim 189, wherein said antifungal agent comprises a macrolide.

193. The method of claim 189, wherein said antifungal agent comprises an azole.

194. The method of claim 189, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

195. The method of claim 189, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

196. The method of claim 195, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

197. The method of claim 196, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

198. The method of claim 189, wherein said formulation comprises a plurality of antifungal agents.

199. The method of claim 189, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

200. The method of claim 189, wherein said effective frequency of said direct mucoadministration is from about four times a day to about once every other week.

201. The method of claim 189, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

202. The method of claim 189, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

203. The method of claim 189, wherein said effective duration is greater than about 30 days.

204. The method of claim 189, wherein said effective duration is greater than about 60 days.

205. The method of claim 189, wherein said effective duration is greater than about 90 days.

206. The method of claim 189, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

207. The method of claim 206, wherein said mammal had a nasal surgery before said mucoadministration.

208. The method of claim 206, wherein said mammal was nasal surgery-free before said mucoadministration.

209. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent, wherein said effective frequency of said direct mucoadministration is from about four times a day to about once every other week.

210. The method of claim 209, wherein said mammal is a human.

211. The method of claim 209, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

212. The method of claim 209, wherein said antifungal agent comprises a macrolide.

213. The method of claim 209, wherein said antifungal agent comprises an azole.

214. The method of claim 209, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

215. The method of claim 209, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

216. The method of claim 215, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

217. The method of claim 216, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

218. The method of claim 209, wherein said formulation comprises a plurality of antifungal agents.

219. The method of claim 209, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

220. The method of claim 209, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

221. The method of claim 209, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

222. The method of claim 209, wherein said effective duration is greater than about 30 days.

223. The method of claim 209, wherein said effective duration is greater than about 60 days.

224. The method of claim 209, wherein said effective duration is greater than about 90 days.

225. The method of claim 209, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

226. The method of claim 225, wherein said mammal had a nasal surgery before said mucoadministration.

227. The method of claim 225, wherein said mammal was nasal surgery-free before said mucoadministration.

228. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

229. The method of claim 228, wherein said mammal is a human.

230. The method of claim 228, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

231. The method of claim 228, wherein said antifungal agent comprises a macrolide.

232. The method of claim 228, wherein said antifungal agent comprises an azole.

233. The method of claim 228, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

234. The method of claim 228, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

235. The method of claim 234, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

236. The method of claim 235, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

237. The method of claim 228, wherein said formulation comprises a plurality of antifungal agents.

238. The method of claim 209, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

239. The method of claim 228, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

240. The method of claim 228, wherein said effective frequency of said direct mucoadministration is more frequent than once a day.

241. The method of claim 228, wherein said effective duration is greater than about 30 days.

242. The method of claim 228, wherein said effective duration is greater than about 60 days.

243. The method of claim 228, wherein said effective duration is greater than about 90 days.

244. The method of claim 228, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

245. The method of claim 244, wherein said mammal had a nasal surgery before said mucoadministration.

246. The method of claim 244, wherein said mammal was nasal surgery-free before said mucoadministration.--

REMARKS

The Examiner rejected claims 1-9, 12-40, 42-46, 48-59, and 70-188, and withdrew claims 10 and 11 from consideration. Claims 1-40, 42-46, 48-59, and 70-188 have been cancelled herein without prejudice. In addition, new claims 189-246 have been added. Thus, claims 189-246 are pending. The specification as filed provides support for new claims 189-246. For example, with respect to independent claim 189, page 59, lines 18-26 as well as Figures 1 and 2 disclose that the presently claimed treatment is effective to reduce or eliminate non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan. In addition, Applicant notes that independent claim 209 contains the limitations set forth in original claims 1 and 31, while independent claim 228 contains the limitations set forth in original claims 1 and 34. Thus, no new matter has been added. In light of the following remarks, Applicant respectfully requests reconsideration and allowance of claims 189-246.

Personal Interview

Applicant's agent thanks Examiner Wang and Primary Examiner Travers for the courtesy of the personal interview on June 12, 2001. The substance of this personal interview involved the issues and arguments presented herein.

Information Disclosure Statement

Applicant respectfully requests return of an initialed copy of the PTO-1449 form filed April 23, 2001. For the Examiner's convenience, a copy of the PTO-1449 form filed April 23, 2001 is attached hereto.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 1-9, 12-40, 42-46, 48, and 70-148 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that:

> Claim 1, 46, 73-75, 101, 102, 106, 145-148, and 151 recite "...non-invasive fungus-induced rhinosinusitis comprising the presence of allergic mucus (or polyp, eosinophilia)..." The sentence is confusing in that it is unclear whether the

presence of the said materials (allergic mucus or polyp, eosinophilia) is a symptom of the rhinosinusitis or the materials are added or obtained by the host. If applicants' intention is the former, following phrase may be considered: "...non-invasive fungus-induced rhinosinusitis, wherein the rhinosinusitis is accompanied with the presence of allergic mucus (or polyp, eosinophilia)..." The claims are indefinite as to how the rhinosinusitis would comprise "allergic mucus (or polyp, eosinophilia)."

Applicant respectfully disagrees. This rejection, however, is moot since claims 1, 46, 73-75, 101, 102, 106, 145-148, and 151 have been cancelled herein. In addition, new claims 189-246 recite the language suggested by the Examiner.

In light of the above, Applicant respectfully submits that new claims 189-246 are free from any rejections under 35 U.S.C. §112.

Rejections under 35 U.S.C. §102(a)

The Examiner rejected claims 1-9, 13-18, 20-21, 30, 40, 46, 73-78, 80-85, 100, 149-154, 156-161, and 184-185 under 35 U.S.C. §102(a) as being anticipated by Bent and Kuhn (*Laryngoscope*, 106:1331-1334 (1996)) and Bent and Kuhn (*Allergy and Asthma Proc.*, 17:259-268 (1996)).

Applicant respectfully disagrees. Original claims 1-9, 13-18, 20-21, 30, 40, 46, 73-78, 80-85, 100, 149-154, 156-161, and 184-185 are not anticipated by either Bent and Kuhn reference. To further prosecution, however, claims 1-9, 13-18, 20-21, 30, 40, 46, 73-78, 80-85, 100, 149-154, 156-161, and 184-185 have been cancelled herein. Thus, this rejection is moot.

New claim 189 requires the recited treatment method to reduce or eliminate the non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan. At no point does Bent and Kuhn's *Larynoscope* reference or *Allergy and Asthma Proceedings* reference disclose such a method. In fact, the only treatment attempted in the Bent and Kuhn references was unsuccessful. Thus, neither Bent and Kuhn reference anticipates new claim 189.

New claim 209 recites the limitations of original claim 31. As indicated above, the Examiner acknowledged that original claim 31 is not anticipated by either Bent and Kuhn reference. Thus, neither Bent and Kuhn reference anticipates new claim 209.

Likewise, new claim 228 recites the limitations of original claim 34. As indicated above, the Examiner acknowledged that original claim 34 is not anticipated by either Bent and Kuhn reference. Thus, neither Bent and Kuhn reference anticipates new claim 228.

In light of the above, Applicant respectfully submits that new claims 189-246 are free from any rejections under 35 U.S.C. §102.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 1-9, 12-40, 42-46, 48-59, and 70-188 under 35 U.S.C. §103(a) as being unpatentable over Bent and Kuhn (*Laryngoscope*, 106:1331-1334 (1996)) and Bent and Kuhn (*Allergy and Asthma Proc.*, 17:259-268 (1996)) in view of Cody *et al.* (*Laryngoscope*, 104:1074-1079 (1994)).

Applicant respectfully disagrees. Original claims 1-9, 12-40, 42-46, 48-59, and 70-188 are not obvious in light of the cited references. To further prosecution, however, claims 1-9, 12-40, 42-46, 48-59, and 70-188 have been cancelled herein. Thus, this rejection is moot.

Again, claim 189 requires the recited treatment method to reduce or eliminate the non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan. At no point do the cited references, either alone or in combination, suggest such a treatment method. In fact, the combination of cited references never suggests the amount, frequency, and duration of a single treatment regimen that involves an antifungal agent, let alone a treatment regimen that reduces or eliminates the non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan. In addition, the combination of cited references fails to provide a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan. In fact, the only attempted topical use of an antifungal agent to treat non-invasive fungus-induced rhinosinusitis was reported to be unsuccessful. Thus, a person of ordinary skill in the art reading the cited references would not have had a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan.

A person of ordinary skill in the art reading the cited references also would have understood that the generally accepted allergic fungal sinusitis treatment is surgery or surgery

followed by postoperative systemic steroid use and/or aeration. See, e.g., page 266 of Bent and Kuhn's *Allergy and Asthma Proceedings* reference and page 1078 of the Cody *et al.* reference. Moreover, a person of ordinary skill in the art reading the cited references would have understood that the most promising future allergic fungal sinusitis treatment is allergy desensitization. See, e.g., page 267 of Bent and Kuhn's *Allergy and Asthma Proceedings* reference and the second column on page 1333 of Bent and Kuhn's *Laryngoscope* reference. Thus, the combination of cited references leads the skilled artisan away from using antifungal agents to reduce or eliminate non-invasive fungus-induced rhinosinusitis. In fact, the cited references merely disclosed that topical "antifungal irrigations may play a future role as a supplement to other surgical and medical therapy." See, page 1334 of Bent and Kuhn's *Laryngoscope* reference. Thus, taken together, the cited references do not render claim 189 obvious.

Claim 209 requires the recited treatment method to have a frequency from about four times a day to about once every other week, while claim 228 requires the recited treatment method to have a frequency of more than once a week. At no point do the cited references, either alone or in combination, suggest such a treatment method. In fact, the combination of cited references never suggests the frequency of a topical antifungal treatment that reduces or eliminates non-invasive fungus-induced rhinosinusitis. In addition, the combination of cited references fails to provide a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis as recited in the present claims. In fact, the only attempted topical use of an antifungal agent to treat non-invasive fungus-induced rhinosinusitis was reported to be unsuccessful. Thus, a person of ordinary skill in the art reading the cited references would not have had a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis as recited in the present claims.

Again, a person of ordinary skill in the art reading the cited references would have understood that the generally accepted allergic fungal sinusitis treatment is surgery or surgery followed by postoperative systemic steroid use and/or aeration. See, e.g., page 266 of Bent and Kuhn's *Allergy and Asthma Proceedings* reference and page 1078 of the Cody *et al.* reference. Moreover, a person of ordinary skill in the art reading the cited references would have

understood that the most promising future allergic fungal sinusitis treatment is allergy desensitization. See, e.g., page 267 of Bent and Kuhn's *Allergy and Asthma Proceedings* reference and the second column on page 1333 of Bent and Kuhn's *Laryngoscope* reference. Thus, the combination of cited references leads the skilled artisan away from the use of antifungal agents to reduce or eliminate non-invasive fungus-induced rhinosinusitis. In fact, the cited reference merely disclosed that topical "antifungal irrigations may play a future role as a supplement to other surgical and medical therapy." See, page 1334 of Bent and Kuhn's *Laryngoscope* reference. Thus, taken together, the cited references do not render claims 209 and 228 obvious.

The Examiner also rejected claims 1-9, 12-40, 42-46, 48-59, and 70-188 under 35 U.S.C. §103(a) as being unpatentable over Cody *et al.* (*Laryngoscope*, 104:1074-1079 (1994)) in view of Bent and Kuhn (*Allergy and Asthma Proc.*, 17:259-268 (1996)). Specifically, the Examiner stated that:

> Cody et al. teaches the general methods for treatment of AFS. The methods including nasal administration of antifungal agents or steroids. See, particularly, the treatment on page 1078 and table V page 1079.
>
> Cody et al. does not teach expressly the particular regimen or the particular administration time and duration herein. However, optimization of such results-effecting parameters is considered within the skill of artisan as discussed above. A person of ordinary skill in the art would have been motivated to employ well-known antifungal agents, including azole or mocrolid compounds, optionally in combination with steroid, for treatment of AFS. The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis. Finally, the method of making a composition by mixing or combining ingredients is considered prima facie obvious.

Applicant respectfully disagrees. Original claims 1-9, 12-40, 42-46, 48-59, and 70-188 are not obvious in light of the cited references. To further prosecution, however, claims 1-9, 12-40, 42-46, 48-59, and 70-188 have been cancelled herein. Thus, this rejection is moot.

With respect to new claims 189-246, Applicant respectfully submits the following. The Cody *et al.* reference discloses a table listing nasal antifungal washes as a treatment aimed at local reduction in antigen load. Bent and Kuhn's *Allergy and Asthma Procedings* reference is a review article about allergic fungal sinusitis. Neither reference teaches or suggests a method that reduces or eliminates non-invasive fungus-induced rhinosinusitis as presently claimed. In fact, the combination of references fails to suggest a treatment regimen that reduces or eliminates the non-invasive fungus-induced rhinosinusitis. At no point do the cited references suggest any amount, frequency, or duration of a single treatment regimen that involves an antifungal agent, let alone optimizing any such undisclosed treatment regimen. Moreover, the combination of cited references fails to provide a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis. Again, at no point does the Cody *et al.* reference or the Bent and Kuhn reference disclose an antifungal dosage, a frequency of administration, or a duration of antifungal treatment. In fact, neither cited reference discloses results about treating non-invasive fungus-induced rhinosinusitis with an antifungal agent. Thus, the cited references do not render the presently claimed invention obvious.

In addition, the Examiner rejected claims 75-148 under 35 U.S.C. §103(a) as being unpatentable over Tsushima *et al.* (*Internal Med.*, 35:736-741 (1996)) and Torpoco *et al.* (Medline abstract accession number 76164567) in view of deShazo *et al.* (*J. Allergy Clin. Immunol.*, 99:475-485 (1997)). Specifically, the Examiner stated that:

> Tsushima et al. teaches a method for treating fungus ball, a known non-invasive fungus-induced disorder. The method comprising topically administration of antifungal agents such as amphotericin B or fluconazole. Torpoco teach that fungus ball is known to be with eosinophilia. See the abstract
>
> Tsushima et al. does not teach expressly the particular regimen or the particular administration time and duration herein and the disorder is fungus ball sinusitis. However, a person or ordinary skill in the art would have been motivated to employ the method for treatment of non-invasive fungus-induced sinusitis (fungus ball) because the method is known to be useful against fungus ball. Further, deShazo teaches that mycetoma (fungus ball sinusitis) may have presence of polyps. See particularly the abstract. Further, optimization of such results-effecting parameters is considered within the skill of artisan as discussed

above. A person or ordinary skill in the art would have been motivated to employ well-known antifungal agents, including azole or mocrolid compounds, optionally in combination with steroid, for treatment of AFS. The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis. Finally, the method of making a composition by mixing or combining ingredients is considered prima facie obvious.

Applicant respectfully disagrees. Original claims 75-148 are not obvious in light of the cited references. Again, the invention is directed to the treatment or prevention of non-invasive fungus-induced rhinosinusitis not the treatment or prevention of fungus balls. To further prosecution, however, claims 75-148 have been cancelled herein. Thus, this rejection is moot.

In light of the above, Applicant respectfully submits that new claims 189-246 are free from any rejections under 35 U.S.C. §103.

CONCLUSION

Applicant submits that claims 189-246 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned agent at the telephone number below

if such will advance prosecution of this application. The Commissioner is authorized to charge any fees or credit any overpayments to Deposit Account No. 06-1050.

Respectfully submitted,

Date:_____ DRAFT _____

J. Patrick Finn III, Ph.D.
Reg. No. 44,109

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696
document1

Version with markings to show changes made

Claims 1-40, 42-46, 48-59, and 70-188 have been cancelled without prejudice.

Claims 189-246 have been added as follows.

--189. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan, said formulation comprising an antifungal agent.

190. The method of claim 189, wherein said mammal is a human.

191. The method of claim 189, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

192. The method of claim 189, wherein said antifungal agent comprises a macrolide.

193. The method of claim 189, wherein said antifungal agent comprises an azole.

194. The method of claim 189, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

195. The method of claim 189, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

196. The method of claim 195, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

197. The method of claim 196, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

198. The method of claim 189, wherein said formulation comprises a plurality of antifungal agents.

199. The method of claim 189, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

200. The method of claim 189, wherein said effective frequency of said direct mucoadministration is from about four times a day to about once every other week.

201. The method of claim 189, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

202. The method of claim 189, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

203. The method of claim 189, wherein said effective duration is greater than about 30 days.

204. The method of claim 189, wherein said effective duration is greater than about 60 days.

205. The method of claim 189, wherein said effective duration is greater than about 90 days.

206. The method of claim 189, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

207. The method of claim 206, wherein said mammal had a nasal surgery before said mucoadministration.

208. The method of claim 206, wherein said mammal was nasal surgery-free before said mucoadministration.

209. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent, wherein said effective frequency of said direct mucoadministration is from about four times a day to about once every other week.

210. The method of claim 209, wherein said mammal is a human.

211. The method of claim 209, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

212. The method of claim 209, wherein said antifungal agent comprises a macrolide.

213. The method of claim 209, wherein said antifungal agent comprises an azole.

214. The method of claim 209, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

215. The method of claim 209, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

216. The method of claim 215, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

217. The method of claim 216, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

218. The method of claim 209, wherein said formulation comprises a plurality of antifungal agents.

219. The method of claim 209, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

220. The method of claim 209, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

221. The method of claim 209, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

222. The method of claim 209, wherein said effective duration is greater than about 30 days.

223. The method of claim 209, wherein said effective duration is greater than about 60 days.

224. The method of claim 209, wherein said effective duration is greater than about 90 days.

225. The method of claim 209, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

226. The method of claim 225, wherein said mammal had a nasal surgery before said mucoadministration.

227. The method of claim 225, wherein said mammal was nasal surgery-free before said mucoadministration.

228. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

229. The method of claim 228, wherein said mammal is a human.

230. The method of claim 228, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

231. The method of claim 228, wherein said antifungal agent comprises a macrolide.

232. The method of claim 228, wherein said antifungal agent comprises an azole.

233. The method of claim 228, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

234. The method of claim 228, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

235. The method of claim 234, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

236. The method of claim 235, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

237. The method of claim 228, wherein said formulation comprises a plurality of antifungal agents.

238. The method of claim 209, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

239. The method of claim 228, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

240. The method of claim 228, wherein said effective frequency of said direct mucoadministration is more frequent than once a day.

241. The method of claim 228, wherein said effective duration is greater than about 30 days.

242. The method of claim 228, wherein said effective duration is greater than about 60 days.

243. The method of claim 228, wherein said effective duration is greater than about 90 days.

244. The method of claim 228, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

245. The method of claim 244, wherein said mammal had a nasal surgery before said mucoadministration.

246. The method of claim 244, wherein said mammal was nasal surgery-free before said mucoadministration.--

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Jens Ponikau
Serial No. : 09/177,164
Filed : October 22, 1998
Title : METHODS AND MATERIALS FOR TREATING AND PREVENTING INFLAMMATION OF MUCOSAL TISSUE

Art Unit : 1617
Examiner : S. Wang

Commissioner for Patents
Washington, D.C. 20231

RESPONSE

In response to the action mailed March 13, 2001, please amend the application as follows.

In the claims:

Please cancel claims 1-40, 42-46, 48-59, and 70-188 without prejudice.

Please add new claims 189-246 as follows.

--189. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan, said formulation comprising an antifungal agent.

190. The method of claim 189, wherein said mammal is a human.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231

September 13, 2001
Date of Deposit

Signature

Jill Huso
Typed or Printed Name of Person Signing Certificate

191. The method of claim 189, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

192. The method of claim 189, wherein said antifungal agent comprises a macrolide.

193. The method of claim 189, wherein said antifungal agent comprises an azole.

194. The method of claim 189, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

195. The method of claim 189, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

196. The method of claim 195, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

197. The method of claim 196, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

198. The method of claim 189, wherein said formulation comprises a plurality of antifungal agents.

199. The method of claim 189, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

200. The method of claim 189, wherein said effective frequency of said direct mucoadministration is from about four times a day to about once every other week.

201. The method of claim 189, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

202. The method of claim 189, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

203. The method of claim 189, wherein said effective duration is greater than about 30 days.

204. The method of claim 189, wherein said effective duration is greater than about 60 days.

205. The method of claim 189, wherein said effective duration is greater than about 90 days.

206. The method of claim 189, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

207. The method of claim 206, wherein said mammal had a nasal surgery before said mucoadministration.

208. The method of claim 206, wherein said mammal was nasal surgery-free before said mucoadministration.

209. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent, wherein said effective frequency of said direct mucoadministration is from about four times a day to about once every other week.

210. The method of claim 209, wherein said mammal is a human.

211. The method of claim 209, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

212. The method of claim 209, wherein said antifungal agent comprises a macrolide.

213. The method of claim 209, wherein said antifungal agent comprises an azole.

214. The method of claim 209, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

215. The method of claim 209, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

216. The method of claim 215, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

217. The method of claim 216, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

218. The method of claim 209, wherein said formulation comprises a plurality of antifungal agents.

219. The method of claim 209, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

220. The method of claim 209, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

221. The method of claim 209, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

222. The method of claim 209, wherein said effective duration is greater than about 30 days.

223. The method of claim 209, wherein said effective duration is greater than about 60 days.

224. The method of claim 209, wherein said effective duration is greater than about 90 days.

225. The method of claim 209, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

226. The method of claim 225, wherein said mammal had a nasal surgery before said mucoadministration.

227. The method of claim 225, wherein said mammal was nasal surgery-free before said mucoadministration.

228. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

229. The method of claim 228, wherein said mammal is a human.

230. The method of claim 228, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

231. The method of claim 228, wherein said antifungal agent comprises a macrolide.

232. The method of claim 228, wherein said antifungal agent comprises an azole.

233. The method of claim 228, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

234. The method of claim 228, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

235. The method of claim 234, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

236. The method of claim 235, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

237. The method of claim 228, wherein said formulation comprises a plurality of antifungal agents.

238. The method of claim 209, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

239. The method of claim 228, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

240. The method of claim 228, wherein said effective frequency of said direct mucoadministration is more frequent than once a day.

241. The method of claim 228, wherein said effective duration is greater than about 30 days.

242. The method of claim 228, wherein said effective duration is greater than about 60 days.

243. The method of claim 228, wherein said effective duration is greater than about 90 days.

244. The method of claim 228, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

245. The method of claim 244, wherein said mammal had a nasal surgery before said mucoadministration.

246. The method of claim 244, wherein said mammal was nasal surgery-free before said mucoadministration.--

REMARKS

The Examiner rejected claims 1-9, 12-40, 42-46, 48-59, and 70-188, and withdrew claims 10 and 11 from consideration. Claims 1-40, 42-46, 48-59, and 70-188 have been cancelled herein without prejudice. In addition, new claims 189-246 have been added. Thus, claims 189-246 are pending. The specification as filed provides support for new claims 189-246. For example, with respect to independent claim 189, page 59, lines 18-26 as well as Figures 1 and 2 disclose that the presently claimed treatment is effective to reduce or eliminate non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan. In addition, Applicant notes that independent claim 209 contains the limitations set forth in original claims 1 and 31, while independent claim 228 contains the limitations set forth in original claims 1 and 34. Thus, no new matter has been added. In light of the following remarks, Applicant respectfully requests reconsideration and allowance of claims 189-246.

Examiner Interviews

Applicant's agent thanks Examiner Wang and Primary Examiner Travers for the courtesy of the personal interview on June 12, 2001. The substance of this personal interview involved the issues and arguments presented herein.

Applicant's agent also thanks Examiner Wang for the courtesy of the telephonic interviews on August 29, 2001 and August 30, 2001. The substance of these telephonic interviews involved the issues and arguments presented herein. With respect to the August 30, 2001 telephonic interview, the following two points were agreed upon. First, with respect to the Bent and Kuhn *Laryngoscope*, 106:1331-1334 (1996) reference, the Examiner agreed that no patient treatments were conducted other than (1) the attempted intraoperative and postoperative topical irrigations with fluconazole without success and (2) the stated "limited experience" with a ketoconazole solution that led the authors to conclude that the solution "does not appear to cause any irritation of nasal mucous membranes." Second, the Examiner agreed that present claim 189 appears free from any 35 U.S.C. §102 rejections.

Information Disclosure Statement

Applicant respectfully requests return of an initialed copy of the PTO-1449 form filed April 23, 2001. For the Examiner's convenience, a copy of the PTO-1449 form filed April 23, 2001 is attached hereto.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 1-9, 12-40, 42-46, 48, and 70-148 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that:

> Claim 1, 46, 73-75, 101, 102, 106, 145-148, and 151 recite "...non-invasive fungus-induced rhinosinusitis comprising the presence of allergic mucus (or polyp, eosinophilia)..." The sentence is confusing in that it is unclear whether the presence of the said materials (allergic mucus or polyp, eosinophilia) is a symptom of the rhinosinusitis or the materials are added or obtained by the host. If applicants' intention is the former, following phrase may be considered: "...non-invasive fungus-induced rhinosinusitis, wherein the rhinosinusitis is accompanied with the presence of allergic mucus (or polyp, eosinophilia)..." The claims are indefinite as to how the rhinosinusitis would comprise "allergic mucus (or polyp, eosinophilia)."

Applicant respectfully disagrees. This rejection, however, is moot since claims 1, 46, 73-75, 101, 102, 106, 145-148, and 151 have been cancelled herein. In addition, new claims 189-246 recite the language suggested by the Examiner.

In light of the above, Applicant respectfully submits that new claims 189-246 are free from any rejections under 35 U.S.C. §112.

Rejections under 35 U.S.C. §102(a)

The Examiner rejected claims 1-9, 13-18, 20-21, 30, 40, 46, 73-78, 80-85, 100, 149-154, 156-161, and 184-185 under 35 U.S.C. §102(a) as being anticipated by Bent and Kuhn (*Laryngoscope*, 106:1331-1334 (1996)) and Bent and Kuhn (*Allergy and Asthma Proc.*, 17:259-268 (1996)).

Applicant respectfully disagrees. Original claims 1-9, 13-18, 20-21, 30, 40, 46, 73-78, 80-85, 100, 149-154, 156-161, and 184-185 are not anticipated by either Bent and Kuhn reference. To further prosecution, however, claims 1-9, 13-18, 20-21, 30, 40, 46, 73-78, 80-85, 100, 149-154, 156-161, and 184-185 have been cancelled herein. Thus, this rejection is moot.

New claim 189 requires the recited treatment method to reduce or eliminate the non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan. At no point does Bent and Kuhn's *Larynoscope* reference or *Allergy and Asthma Proceedings* reference disclose reducing or eliminating non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan. In fact, the only attempted use of an antifungal agent to treat non-invasive fungus-induced rhinosinusitis disclosed in the Bent and Kuhn references was unsuccessful. Thus, neither Bent and Kuhn reference anticipates new claim 189.

New claim 209 recites the limitations of original claim 31. As indicated above, the Examiner acknowledged that original claim 31 is not anticipated by either Bent and Kuhn reference. Thus, neither Bent and Kuhn reference anticipates new claim 209.

Likewise, new claim 228 recites the limitations of original claim 34. As indicated above, the Examiner acknowledged that original claim 34 is not anticipated by either Bent and Kuhn reference. Thus, neither Bent and Kuhn reference anticipates new claim 228.

In light of the above, Applicant respectfully submits that new claims 189-246 are free from any rejections under 35 U.S.C. §102.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 1-9, 12-40, 42-46, 48-59, and 70-188 under 35 U.S.C. §103(a) as being unpatentable over Bent and Kuhn (*Laryngoscope*, 106:1331-1334 (1996)) and Bent and Kuhn (*Allergy and Asthma Proc.*, 17:259-268 (1996)) in view of Cody *et al.* (*Laryngoscope*, 104:1074-1079 (1994)).

Applicant respectfully disagrees. Original claims 1-9, 12-40, 42-46, 48-59, and 70-188 are not obvious in light of the cited references. To further prosecution, however, claims 1-9, 12-40, 42-46, 48-59, and 70-188 have been cancelled herein. Thus, this rejection is moot.

Again, claim 189 requires the recited treatment method to reduce or eliminate the non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan. At no point do the cited references, either alone or in combination, suggest such a treatment method. In fact, the combination of cited references never suggests the amount, frequency, and duration of a single treatment regimen that involves an antifungal agent, let alone a treatment regimen that reduces or eliminates the non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan. In addition, the combination of cited references fails to provide a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan. In fact, the only attempted topical use of an antifungal agent to treat non-invasive fungus-induced rhinosinusitis was reported to be unsuccessful. Further, the Examiner agreed that no patient treatments were conducted other than (1) the attempted intraoperative and postoperative topical irrigations with fluconazole without success and (2) the stated "limited experience" with a ketoconazole solution that led to the authors to conclude that the solution "does not appear to cause any irritation of nasal mucous membranes." Thus, a person of ordinary skill in the art reading the cited references would not have had a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan.

A person of ordinary skill in the art reading the cited references also would have understood that the generally accepted allergic fungal sinusitis treatment is surgery or surgery followed by postoperative systemic steroid use and/or aeration. See, e.g., page 266 of Bent and Kuhn's *Allergy and Asthma Proceedings* reference and page 1078 of the Cody *et al.* reference. Moreover, a person of ordinary skill in the art reading the cited references would have understood that the most promising future allergic fungal sinusitis treatment is allergy desensitization. See, e.g., page 267 of Bent and Kuhn's *Allergy and Asthma Proceedings* reference and the second column on page 1333 of Bent and Kuhn's *Laryngoscope* reference. Thus, the combination of cited references leads the skilled artisan away from using antifungal agents to reduce or eliminate non-invasive fungus-induced rhinosinusitis. In fact, the cited references merely speculates that topical "antifungal irrigations may play a future role as a supplement to other surgical and medical therapy." See, page 1334 of Bent and Kuhn's

Laryngoscope reference. Thus, taken together, the cited references do not render claim 189 obvious.

Claim 209 requires the recited treatment method to have a frequency from about four times a day to about once every other week, while claim 228 requires the recited treatment method to have a frequency of more than once a week. At no point do the cited references, either alone or in combination, suggest such a treatment method. In fact, the combination of cited references never suggests the frequency of a topical antifungal treatment that reduces or eliminates non-invasive fungus-induced rhinosinusitis. In addition, the combination of cited references fails to provide a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis as recited in the present claims. In fact, the only attempted topical use of an antifungal agent to treat non-invasive fungus-induced rhinosinusitis was reported to be unsuccessful. Thus, a person of ordinary skill in the art reading the cited references would not have had a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis as recited in the present claims.

Again, a person of ordinary skill in the art reading the cited references would have understood that the generally accepted allergic fungal sinusitis treatment is surgery or surgery followed by postoperative systemic steroid use and/or aeration. See, e.g., page 266 of Bent and Kuhn's *Allergy and Asthma Proceedings* reference and page 1078 of the Cody *et al.* reference. Moreover, a person of ordinary skill in the art reading the cited references would have understood that the most promising future allergic fungal sinusitis treatment is allergy desensitization. See, e.g., page 267 of Bent and Kuhn's *Allergy and Asthma Proceedings* reference and the second column on page 1333 of Bent and Kuhn's *Laryngoscope* reference. Thus, the combination of cited references leads the skilled artisan away from the use of antifungal agents to reduce or eliminate non-invasive fungus-induced rhinosinusitis. In fact, the cited reference merely speculates that topical "antifungal irrigations may play a future role as a supplement to other surgical and medical therapy." See, page 1334 of Bent and Kuhn's *Laryngoscope* reference. Thus, taken together, the cited references do not render claims 209 and 228 obvious.

The Examiner also rejected claims 1-9, 12-40, 42-46, 48-59, and 70-188 under 35 U.S.C. §103(a) as being unpatentable over Cody *et al.* (*Laryngoscope*, 104:1074-1079 (1994)) in view of Bent and Kuhn (*Allergy and Asthma Proc.*, 17:259-268 (1996)). Specifically, the Examiner stated that:

> Cody et al. teaches the general methods for treatment of AFS. The methods including nasal administration of antifungal agents or steroids. See, particularly, the treatment on page 1078 and table V page 1079.
>
> Cody et al. does not teach expressly the particular regimen or the particular administration time and duration herein. However, optimization of such results-effecting parameters is considered within the skill of artisan as discussed above. A person of ordinary skill in the art would have been motivated to employ well-known antifungal agents, including azole or mocrolid compounds, optionally in combination with steroid, for treatment of AFS. The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis. Finally, the method of making a composition by mixing or combining ingredients is considered prima facie obvious.

Applicant respectfully disagrees. Original claims 1-9, 12-40, 42-46, 48-59, and 70-188 are not obvious in light of the cited references. To further prosecution, however, claims 1-9, 12-40, 42-46, 48-59, and 70-188 have been cancelled herein. Thus, this rejection is moot.

With respect to new claims 189-246, Applicant respectfully submits the following. The Cody *et al.* reference discloses a table listing nasal antifungal washes as a treatment aimed at local reduction in antigen load. Bent and Kuhn's *Allergy and Asthma Proceedings* reference is a review article about allergic fungal sinusitis. Neither reference teaches or suggests a method that reduces or eliminates non-invasive fungus-induced rhinosinusitis as presently claimed. In fact, the combination of references fails to suggest a treatment regimen that reduces or eliminates the non-invasive fungus-induced rhinosinusitis. At no point do the cited references suggest any amount, frequency, or duration of a single treatment regimen that involves an antifungal agent, let alone optimizing any such undisclosed treatment regimen. Moreover, the combination of cited references fails to provide a reasonable expectation of success in achieving reduction or

elimination of the non-invasive fungus-induced rhinosinusitis. Again, at no point does the Cody *et al.* reference or the Bent and Kuhn reference disclose an antifungal dosage, a frequency of administration, or a duration of antifungal treatment. In fact, neither cited reference discloses results about treating non-invasive fungus-induced rhinosinusitis with an antifungal agent. Thus, the cited references do not render the presently claimed invention obvious.

In addition, the Examiner rejected claims 75-148 under 35 U.S.C. §103(a) as being unpatentable over Tsushima *et al.* (*Internal Med.*, 35:736-741 (1996)) and Torpoco *et al.* (Medline abstract accession number 76164567) in view of deShazo *et al.* (*J. Allergy Clin. Immunol.*, 99:475-485 (1997)). Specifically, the Examiner stated that:

> Tsushima et al. teaches a method for treating fungus ball, a known non-invasive fungus-induced disorder. The method comprising topically administration of antifungal agents such as amphotericin B or fluconazole. Torpoco teach that fungus ball is known to be with eosinophilia. See the abstract
>
> Tsushima et al. does not teach expressly the particular regimen or the particular administration time and duration herein and the disorder is fungus ball sinusitis. However, a person or ordinary skill in the art would have been motivated to employ the method for treatment of non-invasive fungus-induced sinusitis (fungus ball) because the method is known to be useful against fungus ball. Further, deShazo teaches that mycetoma (fungus ball sinusitis) may have presence of polyps. See particularly the abstract. Further, optimization of such results-effecting parameters is considered within the skill of artisan as discussed above. A person or ordinary skill in the art would have been motivated to employ well-known antifungal agents, including azole or mocrolid compounds, optionally in combination with steroid, for treatment of AFS. The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis. Finally, the method of making a composition by mixing or combining ingredients is considered prima facie obvious.

Applicant respectfully disagrees. Original claims 75-148 are not obvious in light of the cited references. Again, the invention is directed to the treatment or prevention of non-invasive fungus-induced rhinosinusitis, not the treatment or prevention of fungus balls. To further prosecution, however, claims 75-148 have been cancelled herein. Thus, this rejection is moot.

In light of the above, Applicant respectfully submits that new claims 189-246 are free from any rejections under 35 U.S.C. §103.

CONCLUSION

Applicant submits that claims 189-246 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned agent at the telephone number below if such will advance prosecution of this application. Filed herewith is a check in payment of the Petition for Automatic Extension with the required fee. The Commissioner is authorized to charge any fees or credit any overpayments to Deposit Account No. 06-1050.

Respectfully submitted,

Date: September 13, 2001

J. Patrick Finn III, Ph.D.
Reg. No. 44,109

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696
60053489.doc

Version with markings to show changes made

In the claims

Claims 1-40, 42-46, 48-59, and 70-188 have been cancelled without prejudice.

Claims 189-246 have been added as follows.

--189. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan, said formulation comprising an antifungal agent.

190. The method of claim 189, wherein said mammal is a human.

191. The method of claim 189, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

192. The method of claim 189, wherein said antifungal agent comprises a macrolide.

193. The method of claim 189, wherein said antifungal agent comprises an azole.

194. The method of claim 189, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

195. The method of claim 189, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

196. The method of claim 195, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

197. The method of claim 196, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

198. The method of claim 189, wherein said formulation comprises a plurality of antifungal agents.

199. The method of claim 189, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

200. The method of claim 189, wherein said effective frequency of said direct mucoadministration is from about four times a day to about once every other week.

201. The method of claim 189, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

202. The method of claim 189, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

203. The method of claim 189, wherein said effective duration is greater than about 30 days.

204. The method of claim 189, wherein said effective duration is greater than about 60 days.

205. The method of claim 189, wherein said effective duration is greater than about 90 days.

206. The method of claim 189, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

207. The method of claim 206, wherein said mammal had a nasal surgery before said mucoadministration.

208. The method of claim 206, wherein said mammal was nasal surgery-free before said mucoadministration.

209. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent, wherein said effective frequency of said direct mucoadministration is from about four times a day to about once every other week.

210. The method of claim 209, wherein said mammal is a human.

211. The method of claim 209, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

212. The method of claim 209, wherein said antifungal agent comprises a macrolide.

213. The method of claim 209, wherein said antifungal agent comprises an azole.

214. The method of claim 209, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

215. The method of claim 209, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

216. The method of claim 215, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

217. The method of claim 216, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

218. The method of claim 209, wherein said formulation comprises a plurality of antifungal agents.

219. The method of claim 209, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

220. The method of claim 209, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

221. The method of claim 209, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

222. The method of claim 209, wherein said effective duration is greater than about 30 days.

223. The method of claim 209, wherein said effective duration is greater than about 60 days.

224. The method of claim 209, wherein said effective duration is greater than about 90 days.

225. The method of claim 209, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

226. The method of claim 225, wherein said mammal had a nasal surgery before said mucoadministration.

227. The method of claim 225, wherein said mammal was nasal surgery-free before said mucoadministration.

228. A method for treating a mammal having non-invasive fungus-induced rhinosinusitis, wherein said non-invasive fungus-induced rhinosinusitis is accompanied by the presence of allergic mucus, said method comprising directly mucoadministering to at least a portion of the nasal-paranasal anatomy of said mammal a formulation in an amount, at a frequency, and for a duration effective to reduce or eliminate said non-invasive fungus-induced rhinosinusitis, said formulation comprising an antifungal agent, wherein said effective frequency of said direct mucoadministration is more frequent than once a week.

229. The method of claim 228, wherein said mammal is a human.

230. The method of claim 228, wherein said direct mucoadministration comprises irrigating said nasal-paranasal anatomy with a liquid form of said formulation.

231. The method of claim 228, wherein said antifungal agent comprises a macrolide.

232. The method of claim 228, wherein said antifungal agent comprises an azole.

233. The method of claim 228, wherein said antifungal agent comprises an antifungal agent selected from the group consisting of amphotericin B, ketoconazole, itraconazole, saperconazole, and voriconazole.

234. The method of claim 228, wherein said formulation comprises a pharmaceutically acceptable aqueous vehicle.

235. The method of claim 234, wherein said formulation comprises about 1 ng to about 1000 mg of said antifungal agent per liter.

236. The method of claim 235, wherein said effective amount comprises about 5 mL to about 100 mL of said formulation per nostril of said mammal.

237. The method of claim 228, wherein said formulation comprises a plurality of antifungal agents.

238. The method of claim 209, wherein said effective amount of said formulation comprises about 0.01 ng to about 1000 mg of said antifungal agent per kg of body weight of said mammal.

239. The method of claim 228, wherein said effective frequency of said direct mucoadministration is from about twice a day to about once a week.

240. The method of claim 228, wherein said effective frequency of said direct mucoadministration is more frequent than once a day.

241. The method of claim 228, wherein said effective duration is greater than about 30 days.

242. The method of claim 228, wherein said effective duration is greater than about 60 days.

243. The method of claim 228, wherein said effective duration is greater than about 90 days.

244. The method of claim 228, wherein said mucoadministration begins during a period noncoincident with an intraoperative period, said intraoperative period being the time during a nasal surgery.

245. The method of claim 244, wherein said mammal had a nasal surgery before said mucoadministration.

246. The method of claim 244, wherein said mammal was nasal surgery-free before said mucoadministration.--

MSE
JXF

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/177,164	10/22/1998	JENS PONIKAU	07039/104001	2760

7590 12/17/2001

MARK S ELLINGER
FISH & RICHARDSON
SUITE 3300
60 SOUTH SIXTH STREET
MINNEAPOLIS, MN 55402

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EXAMINER	
WANG, SHENGJUN	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 12/17/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

DOCKETED BY PRACTICE SYSTEMS
ACTION: Early Response - Final
BASE: 12-17-01
DUE: 2-17-02
DEADLINE: 2-17-02
INITIALS: JM

DOCKETED BY PRACTICE SYSTEMS
ACTION: Final Rej / Ntc. of Appeal
BASE: 12-17-01
DUE: 3-17-02
DEADLINE: 6-17-02
INITIALS: AM

Docketed By Billing Secretary/Hnding
Due Date: 3/17/02
Deadline: 3/17/02
Initials: AMS 12/21/01

Docketed By Billing Secretary/Hnding
Due Date: 3/17/02
Deadline: 6/17/02
Initials: AMS 12/21/01

Report OA to Client: 1-7-02

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/177,164	PONIKAU, JENS	
	Examiner	Art Unit	
	Shengjun Wang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S C § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *189-246* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *189-246* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *29* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of applicants' amendments and remarks submitted October 9, 2001 is acknowledged.

Claim Rejections 35 U.S.C. § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 189-246 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bent III et al. (AA, IDS, August 24, 1999) and Bent III et al. Allergy and Asthma Proc. (AE, IDS July 11, 2000).

1. Bent teaches the use of topical antifungal irrigation in the treatment of allergic fungal sinusitis in human. The antifungal agents are amphortericin B and/or ketoconazole. See, particularly, page 1331, the second column. The discussion on page 1333, second column and the conclusion on page 1334. Bent also teaches a therapeutic antifungal solution of 1mg/mL ketoconazole. See, particularly, page 1333, column 2, second paragraph. Bent III et al. Allergy and Asthma Proc. Teaches that allergic fungal sinusitis inherently process the characteristics including the presence of polyp and allergic mucus. See, particularly, the abstract, page 260, the last paragraph bridging to page 261. Bent III et al. Allergy and Asthma Proc. further teach the usefulness of topical steroid for the AFS. See, particularly, table III on page 266.

1. The cited reference does not teach expressly the particular formulation, duration of time, or the particular effect achieved as claimed herein, such as those observable by a computed topography.

However, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the method of Bent for treatment of AFS patient or to employ the particular formulation herein with the said amount and duration.

2. The optimization of a formulation of a known pharmaceutics agent and its administration amount and duration is considered within the skill of artisan, absent evidence to the contrary. Regarding the functional limitation "effective to reduce said non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan," note argument that such claims are not directed to the old and well known ultimate utility (treating fungus-induced non-invasive rhinosinusitis) for the compounds, e.g., amphortericin B and/or ketoconazole, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." Additionally, where the patent Office has reason to believe that a functionally limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to requires the applicant to prove that the subject matter shown to be in the prior art does not posses the characteristic relied on. In the instant invention, the claims are directed to the ultimate utility set

forth in the prior art, albeit distanced by various biochemical effects. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis. See, e.g., page 1333, column 1, in Bent.

2. Claims 189-246 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cody et al. (AM, IDS March 16, 1999).

3. Cody et al. teaches the general methods for treatment of AFS. The methods including nasal administration of antifungal agents herein or steroids. See, particularly, the treatment on page 1078 and table V on page 1079.

Cody et al. does not teach expressly the particular regimen or the particular administration time and duration herein. However, optimization of such results-effecting parameters is considered within the skill of artisan as discussed above. A person of ordinary skill in the art would have been motivated to employ well-known antifungal agents, including azole or mocrolid compounds, optionally in combination with steroid, for treatment of AFS. The employment of a composition, which is known to be useful in the treatment of a disorder such as

allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis.

3. Regarding the functional limitation "effective to reduce said non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan," note argument that such claims are not directed to the old and well known ultimate utility (treating fungus-induced non-invasive rhinosinusitis) for the compounds, e.g., amphortericin B and/or ketoconazole, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." Additionally, where the patent Office has reason to believe that a functionally limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to requires the applicant to prove that the subject matter shown to be in the prior art does not posses the characteristic relied on. In the instant invention, the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical effects. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the

skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

Applicants' amendments and remarks and amendments submitted December 15, 2000 have been fully considered, but are not persuasive for reasons discussed below.

Applicants assert that there are many other options for treating fungus-induced non-invasive rhinosinusitis and one of ordinary skill in the art would have been led away from the claimed invention. Note the presence of other option of treatments of fungus-induced non-invasive rhinosinusitis does not negative the fact that the method herein is known to one of ordinary skill in the art. Because of the clear teaches or suggestion provided in the prior art, it is prima facie obvious for one of ordinary skill in the art, to employ antifungal agent for treating fungus-induced non-invasive rhinosinusitis topically. The effective amounts, frequency and duration are a matter of optimization, which is within the skill of artisan.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang, Ph.D. whose telephone number is (703) 308-4554. The examiner can normally be reached on Monday-Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, J.D., can be reached on (703) 308-4612. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Shengjun Wang

AU 1617

December 11, 2001

RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Jens Ponikau
Serial No. : 09/177,164
Filed : October 22, 1998
Title : METHODS AND MATERIALS FOR TREATING AND PREVENTING INFLAMMATION OF MUCOSAL TISSUE

Art Unit : 1617
Examiner : S. Wang

Commissioner for Patents
Washington, D.C. 20231

RESPONSE

In response to the action mailed December 17, 2001, please consider the following remarks.

REMARKS

The Examiner rejected claims 189-246, which remain pending. In light of the following remarks, Applicant respectfully requests reconsideration and allowance of claims 189-246.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 189-246 under 35 U.S.C. § 103(a) as being unpatentable over Bent I (Bent and Kuhn, *Laryngoscope*, 106:1331-1334 (1996)) and Bent II (Bent and Kuhn, *Allergy and Asthma Proc.*, 17:259-268 (1996)). Specifically, the Examiner stated that Bent I "teaches the use of topical antifungal irrigation in the treatment of allergic fungal sinusitis in human." The Examiner also stated that Bent I "teaches a therapeutic antifungal solution of 1mg/mL ketoconazole," citing page 1333, column 2, second paragraph. In addition, the Examiner stated that Bent II teaches "that

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

July 3, 2002
Date of Deposit

Judy Wasilkus
Signature

Judy Wasilkus
Typed or Printed Name of Person Signing Certificate

allergic fungal sinusitis inherently process [sic] the characteristics including the presence of polyp and allergic mucus," citing the abstract and page 260, the last paragraph bridging to page 261. After acknowledging that the "cited reference does not teach expressly the particular formulation, duration of time, or the particular effect achieved as claimed herein, such as those observable by a computed topography," the Examiner stated that "it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to employ the method of Bent for treatment of AFS patient or to employ the particular formulation herein with the said amount and duration." Further, the Examiner stated that:

> The optimization of a formulation of a known pharmaceutics agent and its administration amount and duration is considered within the skill of artisan, absent evidence to the contrary. Regarding the functional limitation "effective to reduce said non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan," note argument that such claims are not directed to the old and well known ultimate utility (treating fungus-induced non-invasive rhinosinusitis) for the compounds, e.g., amphortericin B and/or ketoconazole, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior, does not cause a claim drawn to those things to distinguish over the prior art." Additionally, where the Patent Office has reason to believe that a functionally limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. In the instant invention, the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical effects. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.
>
> The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in a article of manufacture or composition useful for topical treatment for allergic fungus sinusitis is

motivated by the prior art since topical irrigation which antifungal agents is known in the treatment of allergic fungus sinusitis. See, e.g., page 1333, column 1, in Bent.

Applicant respectfully disagrees. Proper analysis under 35 U.S.C. § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed process; and (2) whether the prior art would also have revealed that in so carrying out, those of ordinary skill would have a reasonable expectation of success. See, In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). It is axiomatic that in order to establish a *prima facie* case of obviousness, a prior art reference must teach or suggest, alone or in combination with another prior art reference, each and every element of the claimed invention. See e.g., MPEP § 2143. The Federal Circuit warns that "both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure," and that "it is impermissible to use the claimed invention as a 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." See, In re Dow Chemical Co., 837 F.2d 469 (Fed. Cir. 1988); In re Fritch, 972 F.2d 1260 (Fed Cir. 1992).

The presently claimed invention requires the recited treatment method to reduce or eliminate the non-invasive fungus-induced rhinosinusitis. At no point do the cited references, either alone or in combination, suggest such a treatment method. In fact, the combination of cited references never suggests the amount, frequency, and duration of a single treatment regimen that involves an antifungal agent, let alone a treatment regimen that reduces or eliminates the non-invasive fungus-induced rhinosinusitis. In addition, the combination of cited references fails to provide a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis. In fact, the only attempted topical use of an antifungal agent to treat non-invasive fungus-induced rhinosinusitis was reported to be "without success." Further, the Examiner agreed that no patient treatments were conducted other than (1) the attempted intraoperative and postoperative topical irrigations with fluconazole without success and (2) the stated "limited experience" with a ketoconazole solution that led to the authors to

conclude that the solution "does not appear to cause any irritation of nasal mucous membranes." Thus, a person of ordinary skill in the art reading the cited references would not have had a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis as presently claimed.

A person of ordinary skill in the art reading the cited references also would have understood that the generally accepted allergic fungal sinusitis treatment is surgery or surgery followed by postoperative systemic steroid use and/or aeration. See, e.g., page 266 of the Bent II reference and page 1078 of the Cody *et al.* reference. Moreover, a person of ordinary skill in the art reading the cited references would have understood that the most promising future allergic fungal sinusitis treatment is allergy desensitization. See, e.g., the second column on page 1333 of the Bent I reference and page 267 of the Bent II reference. Thus, the combination of cited references leads the skilled artisan away from using antifungal agents to reduce or eliminate non-invasive fungus-induced rhinosinusitis as presently claimed. In fact, the cited references merely speculate that topical "antifungal irrigations may play a future role as a supplement to other surgical and medical therapy." See, page 1334 of the Bent I reference. Thus, taken together, the cited references do not render the presently claimed invention obvious.

Even assuming for the sake of argument that the Examiner established a proper *prima facie* case of obviousness, the claimed invention is nevertheless not obvious as evidenced by the fact that the claimed invention satisfies a long-felt need that was recognized, persistent, and not solved by others. It is well established that the long-felt need is measured from the date the problem is identified, not the date of the most pertinent prior art references. See, e.g., MPEP § 716.04 and *Texas Instruments Inc. v. Int'l Trade Comm'n*, 988 F.2d 1165, 1179 (Fed. Cir. 1993).

In 1983, clinicians discovered a new form of chronic sinusitis now known as allergic fungal sinusitis. See, Katzenstien *et al.*, *J. Allergy Clin. Immunol.*, 72:89-93 (1983). Shortly thereafter, clinicians recognized the need for a treatment more effective than surgery and/or steroid treatments, since surgery alone often resulted in multiple disease recurrences while surgery plus steroid use posed significant health risks given the known problems associated with steroid use. For example, according to Katzenstien *et*

al., multiple disease "recurrences were common in our cases after surgical drainage procedures." See, second full paragraph on page 93 of Katzenstien *et al.*, *J. Allergy Clin. Immunol.*, 72:89-93 (1983).

This need for an effective AFS treatment that improves upon the sub-optimal invasive surgery and/or steroid procedures persisted throughout the 1980s and into the 1990s. For example, in 1989, Robson *et al.* stated that:

> The optimal management of allergic fungal sinusitis is controversial and is further confused by reports where invasive and noninvasive fungal sinusitis coexist. Surgery is almost always indicated to remove impacted plugs and to restore and maintain adequate drainage of sinus cavities. The importance of this case is the analogy drawn between the pathogenesis of ABPA and allergic fungal rhinosinusitis, and thus the initiation of therapy with prednisone and topical steroids.

See, page 353 of Robson *et al.*, *Aust. NZ J. Med.*, 19:351-353 (1989). In 1990, Ence *et al.* stated that:

> The optimal treatment of AFS is not yet known. Restoration of sinus aeration and drainage is of obvious importance. This can be accomplished in many cases by either conventional sinus surgery or functional endoscopic sinus surgery. . . . A significant number of patients have recurrences despite what is felt to be adequate sinus surgery. Understanding that AFS is a hypersensitivity reaction and not an invasive process lends support to the use of systemic corticosteroids.

See, second and third full paragraph on page 177 of Ence *et al.*, *Am. J. Rhinol.*, 4:169-178. In 1991, Allphin *et al.* stated that:

> Defining effective treatment strategies for AFS is a difficult task. Surgical drainage and removal of sinus disease should be an initial step, both from a diagnostic and therapeutic standpoint. Whether a traditional external approach or a functional endoscopic approach is chosen is decided on an individual basis. Recurrence of disease despite adequate surgical drainage and aeration of the sinuses is common. Evidence is mounting that systemic corticosteroids are indicated postoperatively in many patients with AFS, especially with extensive recurrent disease and severe atopy.

See, fourth full paragraph on page 819 of Allphin *et al.*, *Laryngoscope*, 101:815-820 (1991). In 1994, the same authors of the references cited by the Examiner, Bent and Kuhn, stated that:

> AFS is the most recently described, common, and controversial of these four [fungal sinusitis] entities. It begins with fungal colonization of the paranasal sinuses, leading to an intense immune response. This results in multiple symptoms for which no reliable treatments exist.

See, first paragraph on page 580 of Bent and Kuhn, *Otolaryngol. Head Neck Surg.* 111:580-588 (1994). Bent and Kuhn also stated that:

> The current treatment of choice for AFS consists of functional endoscopic sinus surgery with debridement of impacted mucin and aeration of diseased sinuses. All patients should experience rapid relief of congestion, drainage, headache, and other associated symptoms. However, this improvement is often transitory. . . . Systemic steroids are recommended in ABPA and have been used successfully in cases of recurrent AFS. However, steroids have multiple well-known side effects, and there are currently no prospective studies to support their use.

See, second and third paragraphs on page 584 of Bent and Kuhn, *Otolaryngol. Head Neck Surg.* 111:580-588 (1994). In 1996, a group of authors including Bent and Kuhn stated that:

> Treatment of allergic fungal sinusitis requires both surgical and medical management. The currently preferred surgical approach is functional endoscopic sinus surgery with complete removal of impacted fungal debris and ventilation of the involved sinuses. . . . Current medical management consists of the use of systemic steroids.

See, sixth and seventh paragraphs on page 134 of Morpeth *et al.*, *Ann. Allergy Asthma Immunol.*, 76:128-140 (1996). Thus, it is clear from the above articles that clinicians were in persistent need of an effective AFS treatment that improves upon the sub-optimal invasive surgery and/or steroid procedures.

Applicant's presently claimed invention fulfills this long-felt need. For example, present claim 189 recites a treatment method that itself effectively reduces or eliminates non-invasive fungus-induced rhinosinusitis. This method obviates the need for surgery

and/or steroid use, although surgery could be used, for example, to clear obstructions that might otherwise impair antifungal agent delivery. Applicant's specification provides multiple working examples demonstrating the effective treatment of non-invasive fungus-induced rhinosinusitis. In fact, Applicant's specification discloses the successful use of antifungal agents to treat non-invasive fungus-induced rhinosinusitis patients who had had no previous nasal surgeries as well as non-invasive fungus-induced rhinosinusitis patients who had had previous nasal surgeries. See, e.g., Example 3, Table II on pages 63-64, and Example 4. Applicant's specification also discloses the successful use of antifungal agents to treat non-invasive fungus-induced rhinosinusitis patients who had had no previous steroid therapy as well as non-invasive fungus-induced rhinosinusitis patients who had had previous topical steroid therapy or previous topical steroid therapy in combination with systemic steroid therapy. See, e.g., Table II on pages 63-64. Thus, a person having ordinary skill in the art reading Applicant's specification would have understood that Applicant's invention provides an effective AFS treatment that drastically improves upon the previous invasive surgery and/or steroid procedures.

Moreover, no one other than Applicant fulfilled this long-felt need prior to Applicant's invention. In fact, prior work has characterized the topical use of antifungal compounds has being "not required," "intriguing, but not well studied," "unwarranted," and "unproven." For example, in 1989, Robson *et al.* stated that:

> the general consensus is that while perioperative amphotericin cover is indicated when the extent of fungal spread is uncertain, long term systemic or local antifungal therapy is not required for noninvasive disease.

See, page 353 of Robson *et al.*, *Aust. NZ J. Med.*, 19:351-353 (1989). In 1990, Ence *et al.* stated that the "role of topical antifungal agents is intriguing but not well studied." See, fourth full paragraph on page 177 of Ence *et al.*, *Am. J. Rhinol.*, 4:169-178. In 1991, Allphin *et al.* stated that:

> Antifungal agents are unwarranted in the allergic disease state without tissue invasion. If pathologic evidence of allergic mucin is found, with or without fungi as seen on fungal stain or culture, initiation of topical intranasal corticosteroids and a complete allergic surveillance are recommended.

See, fifth full paragraph on page 819 of Allphin *et al.*, *Laryngoscope*, 101:815-820 (1991). In 1994, the same authors of the references cited by the Examiner, Bent and Kuhn, stated that:

> Topical and systemic antifungals are even more controversial [than steroid use]. Absolutely no indication exists for the use of toxic antifungal agents such as amphotericin B to treat noninvasive fungal sinusitis. . . . Topical antifungal irrigation solutions may play a role in eliminating residual fungal antigens, but no data are available regarding their clinical usage.

See, third full paragraph on page 585 of Bent and Kuhn, *Otolaryngol. Head Neck Surg.* 111:580-588 (1994). In 1996, a group of authors including Bent and Kuhn stated that "[t]opical or selected systemic antifungal agents may be used, but their efficacy is unproven." See, seventh full paragraph on page 134 of Morpeth *et al.*, *Ann. Allergy Asthma Immunol.*, 76:128-140 (1996). Thus, it is clear from the above articles that the long-felt need for an effective AFS treatment that improves upon invasive surgery and/or steroid procedures was not met.

In addition, the work disclosed in the two Bent and Kuhn references cited by the Examiner did not meet this long-felt need. In fact, at no point do the Bent and Kuhn references disclose an effective AFS treatment that improves upon invasive surgery and/or steroid procedures. This is evidenced by the Bent I reference, a publication presenting *in vitro* fungal susceptibility data, where the authors speculate that "[t]opical antifungal irrigations may play a future role as a supplement to other surgical and medical therapy," while reporting their early phase attempt with "intraoperative and postoperative topical irrigations with fluconazole without success." In the Bent II reference, a review article about four types of fungal sinusitis, the same authors stated that most "authorities concur that functional endoscopic sinus surgery (FESS) with complete removal of inspissated fungi and debris is indicated" and steroids "are being used with increased frequency postoperatively." See, first and second full paragraphs of page 266 of Bent II. Although Bent II cites the *in vitro* analysis of fungal susceptibilities of the Bent I reference, it adds nothing to support the speculations of Bent I. Thus, a person having

ordinary skill in the art reading both Bent and Kuhn references would have appreciated that these authors did not fulfill the long-felt need for an effective AFS treatment that improves upon invasive surgery and/or steroid procedures. In fact, a person having ordinary skill in the art would have appreciated that (1) killing fungus *in vitro*, (2) attempting intraoperative and postoperative topical irrigations with fluconazole without success, and (3) speculating that topical antifungal irrigations may play a future role as a supplement to other surgical and medical therapies falls far short of fulfilling the long-felt need for an effective AFS treatment that improves upon invasive surgery and/or steroid procedures. Therefore, it is clear that Applicant's presently claimed invention satisfies a long-felt need that was recognized, persistent, and not solved by others. This alone is sufficient to establish that the presently claimed invention is not obvious.

The Examiner also rejected claims 189-246 under 35 U.S.C. § 103(a) as being unpatentable over Cody *et al.* (*Laryngoscope*, 104:1074-1079 (1994)). Specifically, the Examiner stated that:

> Cody et al. teaches the general methods for treatment of AFS. The methods including nasal administration of antifungal agents or steroids. See, particularly, the treatment on page 1078 and table V page 1079.
>
> Cody et al. does not teach expressly the particular regimen or the particular administration time and duration herein. However, optimization of such results-effecting parameters is considered within the skill of artisan as discussed above. A person of ordinary skill in the art would have been motivated to employ well-known antifungal agents, including azole or mocrolid compounds, optionally in combination with steroid, for treatment of AFS. The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis.
>
> Regarding the functional limitation "effective to reduce said non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan," note argument that such claims are not directed to the old and well known ultimate utility (treating fungus-induced non-invasive rhinosinusitis) for the compounds, e.g.,

> amphortericin B and/or ketoconazole, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart (169 USPQ 226 at 229 where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause to those things to distinguish over the prior art." Additionally, where the Patent Office has reason to believe that a functionally limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the Applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. In the instant invention, the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical effects. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

Applicant respectfully disagrees. The Cody *et al.* reference discloses a table listing nasal antifungal washes as a treatment aimed at local reduction in antigen load. The Cody *et al.* reference does not teach or suggest a method that reduces or eliminates non-invasive fungus-induced rhinosinusitis as presently claimed. In fact, at no point does the Cody *et al.* reference suggest any amount, frequency, or duration of a single treatment regimen that involves an antifungal agent, let alone optimizing any such undisclosed treatment regimen. Moreover, the Cody *et al.* reference fails to provide a reasonable expectation of success in achieving reduction or elimination of the non-invasive fungus-induced rhinosinusitis. Again, at no point does the Cody *et al.* reference disclose an antifungal dosage, a frequency of administration, or a duration of antifungal treatment. In fact, the Cody *et al.* reference does not disclose any results about treating non-invasive fungus-induced rhinosinusitis with an antifungal agent. Thus, the Cody *et al.* reference does not render the presently claimed invention obvious.

As set forth above, even assuming for the sake of argument that the Examiner established a proper *prima facie* case of obviousness citing the Cody *et al.* reference, the claimed invention is nevertheless not obvious as evidenced by the fact that the claimed

invention satisfies a long-felt need that was recognized, persistent, and not solved by others. Therefore, it is clear that Applicant's presently claimed invention is not obvious.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 189-246 under 35 U.S.C. § 103(a).

CONCLUSION

Applicant submits that claims 189-246 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned agent at the telephone number below if such will advance prosecution of this application. The Commissioner is authorized to charge any fees or credit any overpayments to Deposit Account No. 06-1050.

Respectfully submitted,

Date: July 3, 2002

J. Patrick Finn III, Ph.D.
Reg. No. 44,109

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696
60090371.doc

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L4: Entry 22 of 23 File: USPT Jun 20, 2000

DOCUMENT-IDENTIFIER: US 6077850 A
TITLE: Substituted benzopyran analogs for the treatment of inflammation

Brief Summary Text (7):
Recently, there has been significant research into some of the roles of cyclooxygenase-2. It has been found that COX-2 is upregulated in benign and malignant tumors (K. Subbaramaiah et al., Proc. Soc. Exp. Biol. Med., 216, 201 (1997)) including lung cancer (T. Hida et al., Anticancer Res., 18, 775-82 (1998)), Barrett's esophagus (K. Wilson, Cancer Res., 58, 2929-34 (1998)) and skin cancer (S. Buckman et al., Carcinogenesis, 19, 723-29 (1998)). It is expressed in airway cells with implication in asthma (P. Barnes et al., Lung Biol. Health Dis., 114, 111-27 (1998)). Cox-2 also has a role in pre-term labor, angiogenesis (M. Tsujii et al. Cell, 93, 705-16 (1998)), vascular rejection (M. Bustos, J. Clin. Invest., 100, 1150-58 (1997)), HIV induced apoptosis (G. Bagetta et al., Biochem. Biophys. Res. Commun., 244, 819-24 (1998)), neurodegeneration (T. SanChya et al., Brain Res., 788, 223-31 (1998)), inflammatory bowel disease, colitis, (I. Singer et al., Gastroenterology, 115, 297-306 (1998)), cerebral ischemia (S. Nogawa et al., Proc. Natl. Acad. Sci., 95, 10966-71 (1998)), hypertension (A. Nasjletti, Hypertension, 31, 194-200 (1997)), among others.

Brief Summary Text (10):
U.S. Pat. No. 5,618,843, to Fisher et al., generically describes acid substituted bicyclic moieties as IIb/IIIA antagonists. WO 94/13659, published Jun. 23, 1994, describes fused benzo compounds for the treatment of CNS disorders. Manrao et al. (J. Indian. Counc. Chem., 12, 38-41 (1996)) describes carboxy coumarinimide derivatives and their antifungal activity. U.S. Pat. No. 5,348,976, to Shibata et al., describes amide substituted benzopyrans as antifungals.

Brief Summary Text (13):
U.S. Pat. No. 5,281,720, to Young et al., describes naphthoic acids as lipoxygenase inhibitors. U.S. Pat. No. 5,348,976, to Shibata et al., describes amide substituted benzopyrans as antifungals. U.S. Pat. No. 5,004,744, to Weissmiller et al., describes 2H-benzopyran-3-carboxylic acid as an intermediate for pesticides. U.S. Pat. No. 4,814,346, to Albert et al., describes 3-phenylbenzopyrans as 5-lipoxygenase inhibitors. U.S. Pat. No. 4,761,425, to Girard and Rokach, describes 4-oxo-benzopyrans as leukotriene antagonists. U.S. Pat. No. 4,609,744, to Young et al., describes 4-oxo-benzopyran-carboxylic acids as leukotriene antagonists. U.S. Pat. No. 5,082,849, to Huang et al., describes 4-oxo-benzopyrans as leukotriene antagonists. WO95/07274, published Mar. 16, 1996, describes 2H-benzopyran-3-carboxylic acid as intermediates. WO88/04654, published Jun. 30, 1988, describes 2H-benzopyran-3-carboxylic acid as intermediates. EP412,939, published Feb. 13, 1991, describes substituted chromenes as 5-lipoxygenase inhibitors. JP2-22272 describes benzopyran-3-carboxylic acids. JP59-29681 describes 8-methoxy-benzopyran-3-carboxylic acid as an intermediate. Bunting et al (Can. J. Chem., 62, 1301-07 (1984)) describes the synthesis of 2-hydroxy-1,2-dihydroquinolines. Ukhin et al (Izv. Akad. Nauk. Ser. Khim., 5, 1222-28 (1996)) describe the synthesis of [2-morpholino-6-nitrobenzopyran]-3-carboxylate. Gupta et al. (Indian J. Chem., 21B, 344-347 (1982)) describe chromene-3-carboxylic acid as an intermediate in the preparation of centrally acting muscle relaxants. Rene and Royer (Eur. J. Med. Chem.--Chim. Ther., 10, 72-78 (1975)) describe the preparation of chromene-3-carboxylic acid. U.S. Pat. No. 4,665,202, to Rimbault et al., describes

2-phenyl substituted flavenes and thioflavenes as 5-lipoxygenase inhibitors. U.S. Pat. No. 5,250,547, to Lochead et al., describes benzopyran derivatives as 5-lipoxygenase inhibitors. Satoh et al. [J. Med. Chem., 36, 3580-94 (1993)] describe substituted chromenes as 5-lipoxygenase inhibitors. U.S. Pat. No. 5,155,130, to Stanton et al. describes substituted chromenes as 5-lipoxygenase inhibitors, and specifically 6-benzyloxy-2H-benzopyran-3-carboxylic acid as an intermediate.

Brief Summary Text (47):
Compounds of the present invention would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other cyclooxygenase-2 mediated disorders, such as, as in analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, UV damage, burns and dermatitis, and from post-operative inflammation including from ophthalmic surgery such as cataract surgery and refractive surgery. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis irritable bowel syndrome and ulcerative colitis. Compounds of the invention would be useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like. The compounds would also be useful in the treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone reorption such as associated with osteoporosis.

Brief Summary Text (53):
Compounds of the invention would be useful for the prevention or treatment of benign and malignant tumors/neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophogeal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell aid basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Preferably, neoplasia is selected from gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreas cancer, ovary cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers. The compounds can also be used to treat the fibrosis which occurs with radiation therapy. The method can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, the method can be used to prevent polyps from forming in patients at risk of FAP.

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L4: Entry 23 of 23 File: USPT Mar 7, 2000

DOCUMENT-IDENTIFIER: US 6034256 A
TITLE: Substituted benzopyran derivatives for the treatment of inflammation

Brief Summary Text (7):
U.S. Pat. No. 5,618,843, to Fisher et al., generically describes acid substituted bicyclic moieties as IIb/IIIA antagonists. WO 94/13659, published Jun. 23, 1994, describes fused benzo compounds for the treatment of CNS disorders. Manrao et al. (J. Indian. Counc. Chem., 12, 38-41 (1996)) describes carboxy coumarinimide derivatives and their antifungal activity. U.S. Pat. No. 5,348,976, to Shibata et al., describes amide substituted benzopyrans as antifungals.

Brief Summary Text (29):
Compounds of the present invention would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other cyclooxygenase-2 mediated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, bursitis, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, burns and dermatitis, and from post-operative inflammation including from ophthalmic surgery such as cataract surgery and refractive surgery. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Compounds of the invention would be useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scierodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like. The compounds would also be useful in the treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compounds would also be useful for the treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, and central nervous system damage resulting from stroke, ischemia and trauma. The compounds of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and liver disease. The compounds would also be useful in the treatment of pain, but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. The compounds would be useful for the treatment of dementias. The term "treatment" includes partial or total inhibition of the dementia, including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, and senile dementia.

Brief Summary Text (32):
Compounds of the invention would be useful for the prevention or treatment of neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophogeal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Preferably, neoplasia is selected from gastrointestinal cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers. The compounds can also be used to treat the fibrosis which occurs with radiation therapy. The method can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, the method can be used to prevent polyps from forming in patients at risk of FAP.

Attorney's Docket No.: 07039-104001

OFFICIAL COMMUNICATION

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FOR THE PERSONAL ATTENTION OF:

EXAMINER S. WANG

GROUP 1617 FAX NO: 703-746-3143

Number of pages including this page 8

Applicant : Jens Ponikau
Serial No. : 09/177,164
Filed : October 22, 1998

Art Unit : 1617
Examiner : S. Wang

FACSIMILE COMMUNICATION

Title : METHODS AND MATERIALS FOR TREATING AND PREVENTING INFLAMMATION OF MUCOSAL TISSUE

Commissioner for Patents
Washington, D.C. 20231

Sir:

Attached to this facsimile communication cover sheet is Express Abandonment Under 37 CFR § 1.138, faxed this 1st day of October, 2002, to Group 1617, the United States Patent and Trademark Office.

Respectfully submitted,

Date: October 1, 2002

J. Patrick Finn III, Ph.D.
Reg. No. 44,109

Fish & Richardson P.C., P.A.
60 South Sixth Street, Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Fax: (612) 288-9696

60107281.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Jens Ponikau
Serial No. : 09/177,164
Filed : October 22, 1998
Title : METHODS AND MATERIALS FOR TREATING AND PREVENTING INFLAMMATION OF MUCOSAL TISSUE

Art Unit : 1617
Examiner : S. Wang

Commissioner for Patents
Washington, D.C. 20231

EXPRESS ABANDONMENT UNDER 37 CFR § 1.138

On August 27, 2002, an Office Action for co-pending U.S. Patent Application Serial No. 09/865,785 was mailed. According to that Office Action, pending claims 51-96 conflict with all the claims of U.S. Patent Application Serial No. 09/177,164, and Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. A copy of the August 27, 2002 Office Action for co-pending U.S. Patent Application Serial No. 09/865,785 is attached hereto.

Applicant hereby expressly abandons U.S. Patent Application Serial No. 09/177,164, filed October 22, 1998, without prejudice against pursuing identical or similar claims in the future. For the record, Applicant respectfully disagrees with the Examiner's allegations set forth in the Office Action mailed September 24, 2002 for U.S. Patent Application Serial No. 09/177,164. Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: October 1, 2002

J. Patrick Finn III, Ph.D.
Reg. No. 44,109

Fish & Richardson P.C., P.A.
60 South Sixth Street, Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696
60105606.doc

CERTIFICATE OF TRANSMISSION BY FACSIMILE

I hereby certify that this correspondence is being transmitted by facsimile to the Patent and Trademark Office on the date indicated below.

October 1, 2002
Date of Transmission

Signature

Judy Wasilkus
Typed or Printed Name of Person Signing Certificate

AA
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UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/865,785	05/25/2001	Jens Ponikau	07039-129002	4865

7590 08/27/2002

MARK S. ELLINGER, PH.D.
Fish & Richardson P.C., P.A.
Suite 3300
60 South Sixth Street
Minneapolis, MN 55402

EXAMINER
WEDDINGTON, KEVIN E

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/27/2002 12

Please find below and/or attached an Office communication concerning this application or proceeding.

Resp to Office Action
8.27.02
11.27.02
2.27.03
RMZ

Due Date: 11/27/02
Deadline: 2/27/03
Initials: DAS 9/4/02

Office Action Summary

Application No.	Applicant(s)
09/865,785	Ponikau [redacted]
Examiner	**Art Unit**
Kevin E. Weddington	1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1 136 (a) In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U S C § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment See 37 CFR 1 704(b)

Status

1) ☒ Responsive to communication(s) filed on *Jul 8, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *51-96* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *51-96* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7 and 1(*
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

Claims 51-96 are presented for examination.

Applicants' information disclosure statements file March 6, 2002 and July 8, 2002; terminal disclaimer filed July 8, 2002; and the response filed July 8, 2002 have been received and entered.

Accordingly, the rejection made under non-statutory double patenting as set forth in the previous Office action at pages 2 and 3 is hereby withdrawn.

Double Patenting

Claims 51-96 of this application conflict with all the claims of Application No. 09/177,164. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claims 51-96 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner K. Weddington whose telephone number is (703) 308-1235.

Kevin E. Weddington
Primary Examiner
Art Unit 1614

K. Weddington

August 26, 2002

DISC
JXF

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D C 20231
www uspto gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/177,164	10/22/1998	JENS PONIKAU	07039/104001	2760

7590 09/24/2002

MARK S ELLINGER
FISH & RICHARDSON
SUITE 3300
60 SOUTH SIXTH STREET
MINNEAPOLIS, MN 55402

EXAMINER
WANG, SHENGJUN

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 09/24/2002 36

Please find below and/or attached an Office communication concerning this application or proceeding.

Docketed By Practice Systems
Action Code: Resp to OA
Base Date: 9.24.02
Due Date: 12.24.02
Deadline: 3.24.03
Initials: RMZ

Docketed By Attorney
Due Date: 12/24/02
Deadline: 3/24/03
Initials: OAS 10/1/02

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/177,164	PONIKAU, JENS	
	Examiner	Art Unit	
	Shengjun Wang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1 136(a) In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U S C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2002* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *189-246* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *189-246* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

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a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *31* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Request for a Continued Examination (RCE) under 37 CFR 1.114 filed on July 9, 2002 based on parent Application No. 09/177164 is acceptable and a RCE has been established. An action on the RCE follows.

Claim Rejections 35 U.S.C. § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 189-246 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bent III et al. (AA, IDS, August 24, 1999) and Bent III et al. Allergy and Asthma Proc. (AE, IDS July 11, 2000).

2. Bent teaches the use of topical antifungal irrigation in the treatment of allergic fungal sinusitis in human. The antifungal agents are amphortericin B and/or ketoconazole. See, particularly, page 1331, the second column. The discussion on page 1333, second column and the conclusion on page 1334. Bent also teaches a therapeutic antifungal solution of 1mg/mL ketoconazole. See, particularly, page 1333, column 2, second paragraph. Bent III et al. Allergy and Asthma Proc. Teaches that allergic fungal sinusitis inherently process the characteristics including the presence of polyp and allergic mucus. See, particularly, the abstract, page 260, the last paragraph bridging to page 261. Bent III et al. Allergy and Asthma Proc. further teach the usefulness of topical steroid for the AFS. See, particularly, table III on page 266.

3. The cited reference does not teach expressly the particular formulation, duration of time, or the particular effect achieved as claimed herein, such as those observable by a computed topography.

However, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the method of Bent for treatment of AFS patient or to employ the particular formulation herein with the said amount and duration.

4. The optimization of a formulation of a known pharmaceutics agent and its administration amount and duration is considered within the skill of artisan, absent evidence to the contrary. Regarding the functional limitation "effective to reduce said non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan," note argument that such claims are not directed to the old and well known ultimate utility (treating fungus-induced non-invasive rhinosinusitis) for the compounds, e.g., amphortericin B and/or ketoconazole, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." Additionally, where the patent Office has reason to believe that a functionally limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to requires the applicant to prove that the subject matter shown to be in the prior art does not posses the characteristic relied on. In the instant invention, the claims are directed to the ultimate utility set

forth in the prior art, albeit distanced by various biochemical effects. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

The employment of a composition, which is known to be useful in the treatment of a disorder such as allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis. See, e.g., page 1333, column 1, in Bent.

5. Claims 189-246 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cody et al. (AM, IDS March 16, 1999).

6. Cody et al. teaches the general methods for treatment of AFS. The methods including nasal administration of antifungal agents herein or steroids. See, particularly, the treatment on page 1078 and table V on page 1079.

Cody et al. does not teach expressly the particular regimen or the particular administration time and duration herein. However, optimization of such results-effecting parameters is considered within the skill of artisan as discussed above. A person of ordinary skill in the art would have been motivated to employ well-known antifungal agents, including azole or mocrolid compounds, optionally in combination with steroid, for treatment of AFS. The employment of a composition, which is known to be useful in the treatment of a disorder such as

allergic fungal sinusitis, in the prevention of the same disorder, is considered clearly obvious, as therapeutic effects would have been reasonably expected. The employment of antifungal compounds herein, in an article of manufacture or composition useful for topical treatment of allergic fungus sinusitis is motivated by the prior art since topical irrigation with antifungal agents in known in the treatment of allergic fungus sinusitis.

7. Regarding the functional limitation "effective to reduce said non-invasive fungus-induced rhinosinusitis in a manner observable by a computed topography scan," note argument that such claims are not directed to the old and well known ultimate utility (treating fungus-induced non-invasive rhinosinusitis) for the compounds, e.g., amphortericin B and/or ketoconazole, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." Additionally, where the patent Office has reason to believe that a functionally limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to requires the applicant to prove that the subject matter shown to be in the prior art does not posses the characteristic relied on. In the instant invention, the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical effects. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the

skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

Response to the Arguments

In response to applicants' argument of long felt need, note establishing long-felt need requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. In re Gershon, 372 F.2d 535, 539, 152 USPQ 602, 605 (CCPA 1967) ("Since the alleged problem in this case was first recognized by appellants, and others apparently have not yet become aware of its existence, it goes without saying that there could not possibly be any evidence of either a long felt need in the . . . art for a solution to a problem of dubious existence or failure of others skilled in the art who unsuccessfully attempted to solve a problem of which they were not aware."); Orthopedic Equipment Co., Inc. v. All Orthopedic Appliances, Inc., 707 F.2d 1376, 217 USPQ 1281 (Fed. Cir. 1983) (Although the claimed invention achieved the desirable result of reducing inventories, there was no evidence of any prior unsuccessful attempts to do so.).

Second, the long-felt need must not have been satisfied by another before the invention by applicant. Newell Companies v. Kenney Mfg. Co., 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988) (Although at one time there was a long-felt need for a "do-it-yourself" window shade material which was adjustable without the use of tools, a prior art product fulfilled the need by using a scored plastic material which could be torn. "[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved".)

Third, the invention must in fact satisfy the long-felt need. In re Cavanagh, 436 F.2d 491, 168 USPQ 466 (CCPA 1971).

Long-felt need is analyzed as of the date the problem is identified and articulated, and there is evidence of efforts to solve that problem, not as of the date of the most pertinent prior art references. Texas Instruments Inc. v. Int'l Trade Comm'n, 988 F.2d 1165, 1179, 26 USPQ2d 1018, 1029 (Fed. Cir. 1993).

The failure to solve a long-felt need may be due to factors such as lack of interest or lack of appreciation of an invention's potential or marketability rather than want of technical know-how. Scully Signal Co. v. Electronics Corp. of America, 570 F.2d 355, 196 USPQ 657 (1st. Cir. 1977).

See also Environmental Designs, Ltd. v. Union Oil Co. of Cal., 713 F.2d 693, 698, 218 USPQ 865, 869 (Fed. Cir. 1983) (presence of legislative regulations for controlling sulfur dioxide emissions did not militate against existence of long-felt need to reduce the sulfur content in the air); In re Tiffin, 443 F.2d 344, 170 USPQ 88 (CCPA 1971) (fact that affidavit supporting contention of fulfillment of a long-felt need was sworn by a licensee adds to the weight to be accorded the affidavit, as long as there is a bona fide licensing agreement entered into at arm's length).

Applicants' assert a long felt need "for a treatment more effective than surgery and/or steroid treatments, since surgery alone often resulted in multiple disease recurrences while surgery plus steroid use posed significant health risks given the known problems associated with steroid use." However, from the data in the specification, no evidence showing applicants have solve this problem. Specifically, no evidence showing the claimed method would be similarly

useful to, if not better than, the surgery method and steroid method, no evidence showing the instant method would preventing the recurrences of sinusitis.

Little valuable information may be extracted from the specification for supporting applicants' assertion of solving the long felt problem. The information provided in table II, as well as pages 60-64, provide little help. It appears that many of the patient in the study was also treated with other method, such as steroid, or surgery, it is no clear indication, which method is responsive to the effect presented therein. There is no data with regard to the recurrence. No comparison showing the claimed method is actually similarly useful to, or better than, surgery or steroid therapy.

Further, note the data is not commensurate in scope with claimed invention. Particularly, the frequency for irrigation in the table is at least one a day. Regarding the establishment of unexpected results, a few notable principles are well settled. It is applicant's burden to explain any proffered data and establish how any results therein should be taken to be unexpected and significant. See MPEP 716.02 (b). The claims must be commensurate in the scope with any evidence of unexpected results. See MPEP 716.02 (d). Further, A DECLARATION UNDER 37 CFR 1.1323 must compare the claimed subject matter with the closest prior art in order to be effective to rebut a prima facie case if obviousness. See, MPEP 716.02 (e).

As explained above, applicants fail to establish a case of long felt need. The claims are properly rejected under 35 U.S.C. 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang, Ph.D. whose telephone number is (703) 308-4554. The examiner can normally be reached on Monday-Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Examiner

PUSCELL TRAVERS
PRIMARY EXAMINER
GROUP 1200

Shengjun Wang

September 19, 2002